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# AN INVESTIGATION OF THE POTENCY OF TINCTURE OF ACONITE *

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The pharmacologic action of aconite indicates that the drug should be of distinct use in the treatment of heart disease. The effect of the active principle of the drug, aconitin, on the mammalian heart was studied by Matthews,[1] who described two stages of aconitin poisoning. During the first stage there was slowing of the heart with weakening of systole. The heart-rate was sometimes reduced one-half or one-third of the original rate with a corresponding lowering of the blood-pressure. These effects seemed to be entirely due to central vagus stimulation, as they disappeared after the administration of atropin or after cutting the vagi. During the second stage tachycardia and arhythmia appeared, apparently caused by the action of the drug directly on the heart muscle. Matthews considers that the drug might be employed therapeutically in such doses that the effects of the first stage alone are obtained, and advocates its use in cases in which it is desirable to stimulate the cardiac inhibitory center without affecting the heart muscle.

Aconitin as such has not been used extensively for therapeutic purposes, but the tincture of aconite has been employed with the hope of obtaining the effects which Matthews predicted. Its use has not been successful, however, as is shown by the experiences of several observers. Thus Rudolf and Cole[2] report that no changes in the heart-rate in patients with various diseases were observed after the administration of a chemically standardized tincture of aconite in doses advised by the British Pharmacopeia. They conclude that the drug is of no value in the usual therapeutic doses. Price,[3] after using aconite obtained

* Submitted for publication Sept. 29, 1914.
* From the Hospital of the Rockefeller Institute for Medical Research.

1. Matthews: A Study of the Action of Aconitin on the Mammalian Heart and Circulation, Jour. Exper. Med., 1897, ii, 593.

2. Rudolf and Cole: The Effects of Medicinal Doses of Aconite upon the Pulse-Rate, Am. Jour. Med. Sc., 1912, cxliv, 788.

3. Price: Recent Advances in the Diagnosis, Prognosis and Treatment of Heart Disease: The Polyograph, Brit. Med. Jour., 1913, i, 477.

from various sources in sixteen cases, including five of heart disease, states that it was never found to have any effect as regards slowing the pulse. Piersol[4] reports but slight effect from the administration of from 15 to 25 drops of the tincture of aconite four times a day to a patient with high blood-pressure, and he is led to question the efficiency of the ordinary doses of the preparation.

My experience with the tincture of aconite as a means of lowering the pulse-rate was obtained in an attempt to influence the tachycardia of exophthalmic goiter. A study of this condition was undertaken on the hypothesis that the tachycardia resulted from a lack of balance between the cardiac accelerators and the vagi and that if the so-called vagus tone could be increased, the cardiac rate would diminish. The attempt to increase the vagus action by means of drugs was but part of the study, and evidence of abnormalities in the nervous control of the cardiac rate was obtained. These, however, will not be discussed at present, as the unexpected results of the administration of aconite prevented the completion of the study.

The tincture of aconite was administered in five cases of exophthalmic goiter, three of which were moderately severe, while two were mild. All of the patients had enlarged thyroids and tremor, while

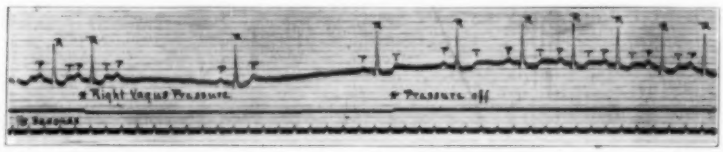


Fig. 1.—Electrocardiogram (Lead 2) showing effect of stimulation of the right vagus nerve by pressure before the administration of the tincture of aconite was begun. Case 2. The R waves in all records have been retouched.

exophthalmos was very marked in two, moderate in two and absent in one case. The pulse-rate after several days' rest in bed ranged from 110 to 120 beats per minute in one case, from 90 to 100 in two, and from 85 to 95 in two cases. In order to ascertain any effect the tincture of aconite might have on the heart in these cases, the pulse-rate was studied under various conditions, both before and during the administration of the drug. These conditions consisted of rest in bed immediately after a constant amount of moderate exercise, and after administration of full doses of atropin. The response of the heart to vagus stimulation by pressure was recorded by means of electrocardiograms, and blood-pressure observations were made daily under as constant

4. Piersol: The Management of High Blood-Pressure, Therap. Gaz., 1913, xxxvii.

conditions as possible. Any symptoms which the drug might cause were watched for.

Besides aconite, the effect of physostigmin in these cases was also studied. Winterberg[5] has shown experimentally that vagus stimulation is more effectual after the administration of this drug, which acts peripherally as regards the vagi, either on the vagus endings or on the heart itself. He suggested that physostigmin might prove useful in cases of tachycardia resulting from lowered vagus tone, and Kaufmann[6] reported favorable results from its use in cases of tachycardia, although it was ineffectual in several cases of exophthalmic goiter. Physostigmin salicylate in a 1 per cent. solution was administered to four of the five patients whom we studied, from 3 to 6 drops three times a day being given. In two cases this drug was given simultaneously with the tincture of aconite. The drug produced indefinite disagreeable sensations with dizziness and faintness before any effect on the cardiac rate was observed, so that its use was discontinued.

The tincture of aconite employed was obtained directly from a firm of manufacturers that has given especial attention to the preparation

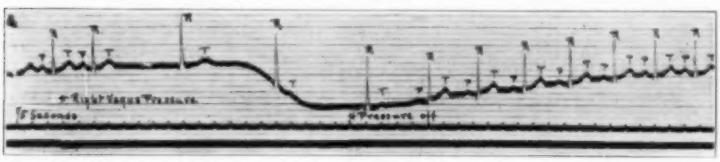

Fig. 2.—The effect of right vagus stimulation when the patient was receiving 7 c.c. tincture of aconite six times a day. Abnormal ventricular complexes are seen during vagus stimulation. Case 2.

of the tincture. The manufacturers cooperated in every way by furnishing the date of chemical assay and all details as to its preparation, as well as suggesting methods of further testing their product. Their assay done shortly before the tincture was obtained showed that it contained 45 mg. aconitin to 100 c.c., thus fulfilling the requirements of the last U. S. Pharmacopeia. The administration to the patients was begun in doses prescribed by the Pharmacopeia, that is, 0.6 c.c. (10 drops) three times a day, 0.27 mg. aconitin being given at each dose. As this dose produced no untoward symptoms and had no effect on the pulse-rate, it was gradually increased until very large doses were administered. The dose in four cases was finally increased to 10 c.c.

5. Winterberg: Ueber die Wirkung des Physostigmin auf das Warmbluterherz, Ztschr. f. exper. Path. u. Therap., 1907, iv, 636.

6. Kaufmann: Physostigmin in Tachycardia, Wien. klin. Wchnschr., 1912, xxv.

(approximately 150 drops) six times a day, and in one case to 7 c.c. (approximately 105 drops) six times a day. Four patients were thus receiving fifteen times the official dose. Instead of receiving 0.27 mg. aconitin, they were supposed to have received 4.5 mg. per dose or 27 mg. in twenty-four hours. This is thirty times the average dose prescribed by the last U. S. Pharmacopeia, though, as will be seen later, they did not receive quite so large an amount of aconitin. The rate at which the doses were increased varied in the different cases, and the maximal dose was reached in from two to six weeks from the onset of the administration.

The effects of these very large doses will be discussed later, but it suffices here to say that no subjective symptoms were observed, and no slowing of the pulse-rate or lowering of the blood-pressure occurred.

In order to determine the reason why the tincture of aconite did not produce the effects which would be expected from the pharmacologic action of aconitin, the tincture was reassayed chemically and a physiologic assay was done.

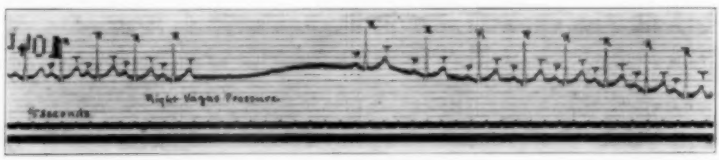


Fig. 3.—The effect of right vagus stimulation eight days after the last dose of tincture of aconite. Abnormal ventricular complexes do not occur. Case 2.

The chemical assay was kindly undertaken by Dr. C. W. Ballard of the College of Pharmacy of the City of New York, Columbia University, to whom I wish to express my gratitude. Dr. Ballard made four assays of the same lot of the tincture which the patients received, using 100 c.c. for each assay. The results indicated by the four assays were as follows:

Sample "A" contained 0.03648 gm. aconitin per 100 c.c.
Sample "B" contained 0.03648 gm. aconitin per 100 c.c.
Sample "C" contained 0.03968 gm. aconitin per 100 c.c.
Sample "D" contained 0.03776 gm. aconitin per 100 c.c.

The average of the four samples, as indicated by the assay, was 0.03760 gm. aconitin per 100 c.c.

It is thus evident that, on the basis of the U. S. P. method of assay, when the tincture of aconite reached Dr. Ballard's laboratory, it contained approximately 38 mg. aconitin per hundred c.c. or 84.4 per cent. of the aconitin required by the U. S. Pharmacopeia (45 mg.). The lack of activity of the tincture could not, therefore, have been caused by this moderate diminution of the aconitin con-

tent, and the analyses showed that the manufacturers had approximately fulfilled the only standard required by the U. S. Pharmacopeia for the tincture of aconite, namely, the aconitin content as shown by chemical assay.

The physiological assay was carried out by the method described by Roth,[7] and consisted in determining the minimal lethal dose of the tincture of aconite for guinea-pigs. The guinea-pigs were weighed and divided into two parallel series, two animals always receiving the same dose. The tincture was given subcutaneously under the skin of the abdomen in increasing doses and was at first used in a 1:50 dilution. According to Roth, 0.00036 c.c. per gram body weight is the lethal dose of the tincture for guinea-pigs. The first experiment was therefore performed as shown in Protocol 1, a dilution of 1:50 being used:

PROTOCOL 1.—PHYSIOLOGICAL ASSAY OF TINCTURE OF ACONITE, EXPERIMENT 1

| First Series | | | | Second Series | | | |
|---|---|---|---|---|---|---|---|
| No. | Weight gm. | Amount Injected c.c. | C.C. Tincture per gm. | No. | Weight gm. | Amount Injected c.c. | C.C. Tincture per gm. |
| 1 | 300 | 2.5 | 0.00030 | 1 | 290 | 2.5 | 0.00034 |
| 2 | 320 | 3.0 | 0.00037 | 2 | 250 | 2.5 | 0.00040 |
| 3 | 280 | 3.5 | 0.00050 | 3 | 250 | 3.0 | 0.00048 |
| 4 | 320 | 4.5 | 0.00056 | 4 | 250 | 3.5 | 0.00056 |
| 5 | 300 | 4.5 | 0.00060 | 5 | 220 | 3.5 | 0.00064 |
| 6 | 270 | 4.6 | 0.00068 | 6 | 220 | 4.0 | 0.00073 |

The guinea-pigs were observed for one hour and then at the end of twelve hours. All survived. The doses administered to the guinea-pigs were gradually increased, the dilution of the tincture being diminished until finally undiluted tincture was employed. It was found that although the drug was at times fatal, guinea-pigs often survived as much of the tincture of aconite as could be conveniently introduced under the skin of the abdomen. This is shown by Protocol 2.

PROTOCOL 2.—PHYSIOLOGICAL ASSAY OF TINCTURE OF ACONITE, EXPERIMENT 2

First Series

| No. | Weight gm. | Amount Injected, c.c. | C.C. Tincture per gm. | Result |
|---|---|---|---|---|
| 1 | 300 | 1.2 | 0.004 | Survived twelve hours |
| 2 | 300 | 1.8 | 0.006 | Died in six hours |
| 3 | 300 | 2.4 | 0.008 | Survived twelve hours |
| 4 | 300 | 3.0 | 0.010 | Died in six hours |
| 5 | 300 | 3.6 | 0.012 | Survived twelve hours |
| 6 | 270 | 3.8 | 0.014 | Died in twelve hours |

7. Roth: The Physiological Assay of Aconite, Jour. Am. Pharm. Assn., 1913, ii, 705.

PROTOCOL 2.—*Continued.*—Second Series

| No. | Weight gm. | Amount Injected, c.c. | C.C. Tincture per gm. | Result |
|---|---|---|---|---|
| 1 | 350 | 1.4 | 0.004 | Survived twelve hours |
| 2 | 350 | 2.1 | 0.006 | Survived twelve hours |
| 3 | 320 | 2.6 | 0.008 | Survived twelve hours |
| 4 | 280 | 3.0 | 0.010 + | Survived twelve hours |
| 5 | 300 | 3.6 | 0.012 | Survived twelve hours |

Guinea-pigs thus survived 0.012 c.c. of the tincture of aconite per gram body weight. As this tincture contained 0.000376 gm. aconitin per c.c., according to Dr. Ballard's analysis, these guinea-pigs survived 0.0000045 gm. aconitin per gram body weight. None of the guinea-pigs in these experiments had been given injections of the tincture previously.

Crystalline aconitin obtained from the same drug firm was tested by the same method. One-tenth of a gram of aconitin was dissolved in 100 c.c. of 2 per cent. acetic acid and then made up to a 1:100,000 solution with sterile 0.85 per cent. sodium chlorid solution. Protocol 3 demonstrates that the minimal lethal dose of the aconitin is at least 0.0000001 gm. per gram guinea-pig.

PROTOCOL 3.—PHYSIOLOGICAL ASSAY OF TINCTURE OF ACONITE, EXPERIMENT 3

First Series

| No. | Weight gm. | Amount Injected, c.c | Aconitin per gm. | Result |
|---|---|---|---|---|
| 1 | 220 | 0.55 | 0.000,000,025 | Survived 12 hours |
| 2 | 220 | 1.10 | 0.000,000,050 | Survived 12 hours |
| 3 | 220 | 1.65 | 0.000,000,075 | Survived 12 hours |
| 4 | 200 | 2.00 | 0.000,000,100 | Died in 35 minutes |
| 5 | 200 | 2.50 | 0.000,000,125 | Died in 30 minutes |

Second Series

| No. | Weight gm. | Amount Injected, c.c | Aconitin per gm. | Result |
|---|---|---|---|---|
| 1 | 200 | 0.5 | 0.000,000,025 | Survived |
| 2 | 200 | 1.0 | 0.000,000,050 | Died in 75 minutes |
| 3 | 190 | 1.4 | 0.000,000,074 | Died in 70 minutes |
| 4 | 180 | 1.8 | 0.000,000,100 | Died in 5 hours |
| 5 | 170 | 2.1 | 0.000,000,124 | Died in 65 minutes |

The guinea-pigs had not received previous injections.

It is seen, therefore, that the guinea-pigs survived a dose of tincture of aconite which, if the U. S. P. assay method were to be relied on, would have contained forty-five times the minimal lethal dose of crystalline aconitin.

To determine whether the presence of the alcohol of the tincture could be a factor in diminishing its toxicity by decomposing the aconitin, the following experiment was performed: Into 66 per cent.

alcohol, the percentage contained in the tincture, crystalline aconitin was introduced in the same amount as that found in the tincture administered to the patients. This alcoholic solution of aconitin was allowed to stand several days, when it was found that the toxicity of the aconitin was the same as that in aqueous solutions. The alcohol of the tincture was apparently not, therefore, a factor in diminishing the toxicity of the solution by decomposing the aconitin contained in it.

The experiments show definitely that there was such a marked difference between the toxicity of the substance in the tincture giving the chemical tests for aconitin and of crystalline aconitin that the two substances cannot be considered identical. Guinea-pigs survived at least forty-five times as much of the former as of the latter. In fact, the dose of the tincture of aconite which would invariably prove fatal was not determined. It is therefore evident that the surprisingly large doses of the tincture of aconite produced no symptoms in patients because it did not contain a substance with the activity of crystalline aconitin, although the chemical assay as required by the

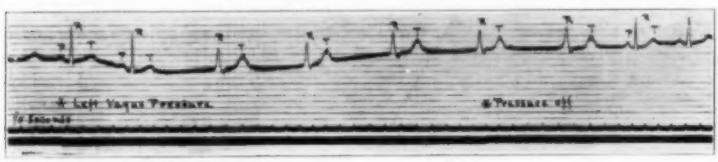

Fig. 4.—Electrocardiogram (Lead 2) showing the effect of stimulation of the left vagus nerve by pressure when the patient had received 10 c.c. tincture of aconite six times a day for five days. Abnormal ventricular complexes during vagus stimulation. Case 3.

U. S. Pharmacopeia indicated that such a substance was present. The cause of this inactivity of the tincture of aconite is not explained.

These facts are brought forward to emphasize the necessity of physiological assays of all drugs which can be so standardized, and also to point out the importance of determining the quality of drugs used before conclusions are drawn as to their effects or the absence of effects. The importance of the so-called "bio-assay" has been pointed out by Wood,[8] who states that the Pharmacopeia requires physiologic standardization of only fifteen drugs out of fifty-three in which such a standardization is possible.

It was previously stated that the large doses of the tincture of aconite produced no subjective symptoms in the five patients with exophthalmic goiter to whom they were administered, and that no

8. Wood: The Purpose and Limitations of Bio-Assay, Jour. Am. Med. Assn., 1912, lix, 1433.

slowing of the pulse-rate or lowering of the blood-pressure occurred. In four of the five cases, however, there was observed an abnormal response of the heart to vagus stimulation when the patients were receiving the largest doses of the tincture. Electrocardiograms taken during stimulation by pressure over the left or the right vagus before the drug was administered showed, in all cases, stoppage of the whole heart, except that occasionally with left vagus pressure, waves of auricular activity appeared independently (Fig. 1). When these procedures were repeated during the administration of maximal doses, the electrocardiograms show that in four cases the response to vagus stimulation had changed. Instead of the absence of waves of ventricular activity during vagus stimulation, there appeared ventricular waves of abnormal form, indicating that ectopic ventricular contractions (extrasystoles) occurred during quiescence of the auricles (Figs. 2 and 4). This abnormal response to vagus stimulation disappeared in all the cases when the drug was stopped (Figs. 3 and 5). It is evident, therefore, that the large doses of the tincture of aconite had an effect on the heart, rendering the ventricles more ready to

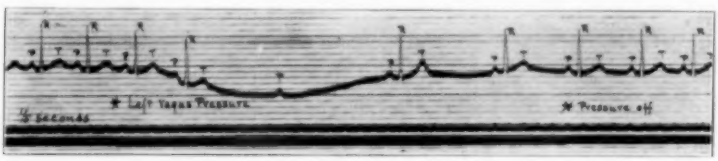

Fig. 5.—The effect of left vagus stimulation four days after the last dose of tincture of aconite. Abnormal ventricular complexes do not occur. Case 3.

contract spontaneously. In other words, the drug apparently increased the irritability of the ventricles.

This effect of the tincture of aconite on the human heart, apparent only during vagus stimulation, resembles the second stage of aconitin action described by Matthews. Similar effects of aconitin on the mammalian heart have been described by Cushny,[9] who found that under the effect of the drug, normally inactive points in the heart take on the power of originating stimuli, the irritability of each part of the heart being augmented.

## SUMMARY

During a study of the tachycardia of exophthalmic goiter, it was found that very large doses of the tincture of aconite produced no subjective symptoms and no slowing of the heart rate. Doses of 10 c.c. (approximately 150 drops) were given six times a day. An attempt to augment the action of aconite by physostigmin was not successful.

Although the chemical assay showed that the tincture used did not fulfil the Pharmacopeial requirements as regards its aconitin content, the discrepancy was not sufficient to account for the impotency of the drug. The physiologic assay showed that the minimal lethal dose for guinea-pigs of a substance giving the chemical tests for aconitin contained in the tincture was at least forty-five times as large as that of crystalline aconitin, and that the alcohol of the tincture apparently played no rôle in diminishing the toxicity of the solution by decomposing the aconitin. This substance in the tincture can hardly, therefore, be considered identical with crystalline aconitin. These facts emphasize the necessity of physiological standardization of the tincture of aconite, which is not now required by the Pharmacopeia. Evidence was obtained that the maximal doses of the tincture of aconite rendered the ventricles more liable to spontaneous contractions, apparently increasing their irritability.

Washington University Medical School.

9. Cushny: Irregularities of the Mammalian Heart Observed Under Aconitin and on Electrical Stimulation, Heart, 1909, i, 1.

# NUCLEAR DIGESTION AND URIC ACID EXCRETION IN A CASE OF TOTAL OCCLUSION OF THE PANCREATIC DUCT *

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The digestion of nuclear material and the production of purin bases therefrom has been discussed from three points of view: (1) the morphological destruction of the nucleus; (2) the digestion of the so-called nucleoproteids and nucleins; and (3) the splitting of nucleic acid. The localization of the third stage, namely, nucleic acid digestion, has been unquestionably settled by the demonstration of a nuclease in the erepsin of a dog (Nakayama,[1] 1904) and of its absence from the gastric and pancreatic juices (Levene and Medigreceanu,[2] 1911). Confirmatory evidence is afforded by the work of London and Schittenhelm[3] (1910) who found no difference in the nucleic acid metabolism of a normal dog as compared with animals in which the stomach or the pancreas had been removed, or those with a ligated pancreatic duct.

The morphological destruction of the nucleus has been the subject of much controversy since the statement of Adolf Schmidt[4] (1899) that the presence of undigested nuclei in the muscle fibers found in the feces was an evidence of decreased or absent pancreatic function. On this finding, Schmidt based a clinical test consisting of the feeding of small pellets of muscle tissue enclosed in silk bags. He recovered the tissue from the stool, sectioned, stained and examined it for nuclei. Intact nuclei were considered evidence of pancreatic achylia. Kashiwado[5] (1911) modified this test by using thymus nuclei isolated by gastric digestion and stained with hematoxylin — these nuclei were mixed with lycopodium spores and administered in capsules. Kashiwado found in test-tube experiments that neither gastric juice (dog), extract of duodenal mucosa or duodenal juice would digest the nuclei, whereas pancreatic juice quickly accomplished this result. Strauch[6] (1910), using muscle tissue, confirmed Kashiwado's results with the

* Submitted for publication Dec. 3, 1914.
* From the Medical Clinic of the Johns Hopkins Hospital.

1. Nakayama: Ztschr. f. physiol. Chem., 1896, xli, 348.
2. Levene and Medigreceanu: Jour. physiol. Chem., 1911, ix, 65.
3. London and Schittenhelm: Ztschr. f. physiol. Chem., 1910, lxx, 10.
4. Schmidt: Deutsch. med. Wchnschr., 1899, No. 49, p. 811.
5. Kashiwado: Deutsch. Arch. f. klin. Med., 1911, civ, 584.
6. Strauch: Deutsch. Arch. f. klin. Med., 1910, ci, 128.

exception that juice pressed from the intestinal wall seemed to have a slightly destructive effect on the nuclei, and Fronzig[7] (1913), using the nuclei of frog's blood, held that his results agreed with the fundamental principle of the Schmidt test. There has, however, been a great deal of evidence pointing to an opposing view. Glaessner and Popper[8] (1908) found that easily stainable nuclei persisted after digestion with the juice obtained from a pancreatic fistula in a girl of 17, while Hesse,[9] as a result of test-tube experiments and of the insertion of a muscle cube into the stomach (1910), claims that gastric juice will digest nuclei. Van Westenrijk[10] (1911) says that, in the dog, muscle tissue is digested *en masse* in the gastro-intestinal tract, and he holds that muscle tissue without nuclei is never to be found, no matter how the factors of digestion be varied. The clinical experience of many observers (Leech,[11] Pratt[12] and others) has been that the Schmidt test is in no way a dependable one, but the author of the test still (July, 1914) considers it of great value.

It was formerly held that the so-called nucleoproteid was a distinct entity, and several observers (Popoff,[13] 1894; Milroy,[14] 1896) demonstrated to their satisfaction that this hypothetical substance was not split by gastric digestion, whereas it was by pancreatic. Even in the 1914 edition of his Lehrbuch der Physiologischen Chemie, Abderhalden assumes two stages of nucleoproteid digestion: first, the formation of "nuclein" from nucleoproteid, accomplished by the stomach, and, secondly, the splitting of "nuclein" into nucleic acid and protein by the activity of the pancreatic juice. This theory of two distinct combinations of nucleic acid with protein has been quite definitely disproved by the work of Umber[15] (1901), who showed that any nucleoproteid is easily split by pepsin or trypsin with the liberation of nucleic acid. Further proof is given by Walter Jones,[16] who demonstrated that the combination of nucleic acid with a protein is merely that of a weak base and a weak acid and is easily reproduced in the test-tube.

When a patient on the medical service of the Johns Hopkins Hospital (whose history is reported below) was found to have a complete absence of pancreatic secretion in the intestinal tract, the idea was conceived that by feeding thymus gland and estimating the increased

7. Fronzig: Ztschr. f. klin. Med., 1913, lxxvii, 84.
8. Glaessner and Popper: Deutsch. Arch. f. klin. Med., 1908, xciv, 46.
9. Hesse: Ztschr. f. exper. Path. u. Therap., 1910, vii, 91.
10. Van Westenrijk: Ztschr. f. exper. Path. u. Therap. 1911, viii, 353.
11. Leech: Practitioner, 1911, lxxxvii, 631.
12. Pratt: Am. Jour. Med. Sc., 1912, cxliii, 313.
13. Popoff: Ztschr. f. physiol., Chem., 1894, xviii, 534.
14. Milroy: Ztschr. f. physiol. Chem., 1896, xxii, 307.
15. Umber: Ztschr. f. klin. Med., 1901, xliii, 282.
16. Jones, Walter: Nucleic Acids (Monographs on Biochemistry, 1914).

output of uric acid in the urine, the possible necessity of the pancreas to any stage of nuclear digestion could be conclusively demonstrated. It has long been known that approximately 50 per cent. of ingested purins is excreted in the urine (Weintraud,[17] 1895, and others).

### CASE REPORT

The patient's history and the clinical findings were as follows:

*History.*—M. W., aged 42 (Med. No. 33,205), a Russian Jew, married, was admitted to the hospital Oct. 20, 1914. The family and personal histories were unimportant. The patient complained of a persistent, painless jaundice (with one slight remission in the first month) lasting for nine months and accompanied by dark urine, rather frequent, soft, clay-colored stools, and 90 pounds loss of weight.

*Examination.*—On examination he was found to be a large-framed man, fairly nourished, but whose skin corroborated the statement of loss of weight. The skin and conjunctivae were intensely jaundiced. The heart and lungs were negative. The liver was large, extending from the sixth rib to the crest of the ilium in the nipple line, smooth, firm and sharp-edged. The gall-bladder was definitely palpated projecting about 2 inches below the liver margin. No other masses were felt; there were no signs of collateral portal circulation. The reflexes were normal. Rectal examination was negative. The temperature, pulse, respiration and blood-pressure were normal.

Blood: White blood-cells, 13,360; polymorphonuclears, 71 per cent.; hemoglobin (Sahli), 83 per cent.; fragility of the red blood-cells, normal; Wassermann reaction, negative; Widal reaction, negative.

Urine: Dark-brown; trace of albumin; few granular casts; bile tests strongly positive.

Stools: Large soft, clay-colored, frequent (while in the hospital the patient averaged three stools daily). Microscopically, marked increase of neutral fats and fatty acids, with the neutral fat clearly predominant; many undigested muscle fibers; hydrobilirubin, negative.

Calmette tuberculin test (1 per cent. and 5 per cent.), negative.

Gastric Analysis: No free HCl; total acidity, 9; no blood or lactic acid; much yeast.

The special pancreatic tests were as follows:

Duodenal contents were obtained with an Einhorn tube and the ferment activities determined by the methods of T. R. Brown.[18]

Trypsin, absent (digestion with 1 per cent. casein solution).
Lipase, absent (digestion with 1 per cent. monobutyrin solution).
Diastase, trace, probably salivary (digestion with one-tenth per cent. soluble starch).

Feces: Brown's[18] technic was used here also.
Trypsin, absent.
Lipase, trace; probably from the lower intestinal tract.
Diastase, absent.

Urine: Diastase, 50 units (high) by Brown's[18] method. Trypsin, absent.
Schmidt-Kashiwado nuclei test, negative (spores recovered).
Blood sugar, 100 mg. per 100 c.c. (normal).
Carbohydrate Tolerance: 100 gm. glucose gave no glycosuria.

17. Weintraud: Berl. klin. Wchnschr., 1895, xxxii, 405.
18. Brown, T. R.: Johns Hopkins Hospital Bulletin, 1914, xxv, No. 281.

The patient was discharged Nov. 4, 1914, with the diagnosis of "carcinoma of the head of the pancreas, obstruction of the common bile duct and obstructive cirrhosis of the liver."

The history of nine months of persistent, painless jaundice, associated with a loss of weight, and the clinical findings of a dilated gall-bladder, acholic stools and bile in the urine, point toward a carcinomatous obstruction of the common bile-duct. The inability to demonstrate any of the pancreatic ferments in either the duodenal juice or the feces, coupled with the frequent, large, fatty stools showing many muscle fibers, justifies the assumption that there was a complete absence of the external secretion of the pancreas from the intestinal tract of this patient.

The following experiment was therefore carried out: October 27, the patient was put on a purin-free diet containing 2,900 calories, and the daily uric acid output of the urine determined by means of the Folin-Schaeffer method. On the fifth day (October 31) 150 gm. of fresh calf's thymus were given with the noon meal and the same amount was given on the sixth day (November 1). The purin-free diet was resumed on the succeeding days. The results are found in the accompanying table.

TABLE SHOWING RESULTS OF EXPERIMENT ON A PURIN-FREE DIET

| Date October | Diet | Total Urine c.c. | Uric Acid gm. |
|---|---|---|---|
| 27 | Purin-free | 1,565 | 0.82 |
| 28 | Purin-fee | 1,418 | 0.76 |
| 29 | Purin-free | 1,420 | 0.76 |
| 30 | Purin-free | 1,380 | 0.51 |
| 31 | Plus 150 gm. of thymus | 1,660 | 1.32 |
| November | | | |
| 1 | Plus 150 gm. of thymus | 1,540 | 1.25 |
| 2 | Purin-free | 1,485 | 0.15 |
| 3 | Purin-free | 1,279 | 0.14 |

The first day's results may be excluded, for a constant level of excretion under the purin-free diet had not been reached at this time. The maximum truly endogenous output was, therefore, 0.76 gm., and the excess of excretion over this amount on the two thymus days was 0.52 gm. and 0.48 gm. By the principle that 50 per cent. of ingested purins is excreted as uric acid in the urine, 150 gm. of calf's thymus should cause an exogenous excretion of approximately 0.6 gm. of uric acid over the endogenous level. It can be safely said, therefore, that there was practically a quantitative recovery of the exogenous uric acid. This finding conclusively demonstrates that there was digestion of thymus nuclei with the production of the uric acid in the urine in the absence of both bile and pancreatic juice.

SUMMARY

The results of this experiment prove that in the human being the digestion of nuclear material, the purin metabolism and the uric acid formation do not depend on the presence of the pancreatic secretion in the intestinal canal. This finding, together with the negative result of the test in this case, and in many other reported cases, definitely points out the worthlessness of the Schmidt nuclear test for pancreatic function.

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# SECONDARY HYPERTROPHIC OSTEO-ARTHROPATHY AND ITS RELATION TO SIMPLE CLUB-FINGERS *

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Since the original papers of Bamberger[12, 13] (1889 and 1891) and Marie[113] (1890) numerous reports have been published which have more and more definitely established this morbid condition as a distinct clinical entity among the general group of allied diseases, including leontiasis ossae, osteitis deformans, acromegaly, rickets, syphilis of the bones and others. Walters[210] (1896), Massalongo[117] (1897), Janeway[88] (1903), Thompson[192] (1904), Wynn[215] (1904), Ebstein[48] (1906) and Alexander[3] (1906) have each collected the typical cases from the literature and given a critical review, together with a general discussion of the diseases. In spite of these and many other excellent reports, much regarding the cause, course and real nature of the pathologic changes remains obscure.

The object of the present report is to record the results of the study of five typical cases for a period of years with reference to such considerations as the extent of involvement of the bones and joints, the nature of the process, the course of the disease, and especially the relation of secondary hypertrophic osteo-arthropathy to simple clubbing of the fingers.

## *Group A.—Five Typical Cases of Secondary Hypertrophic Osteo-Arthropathy*

CASE 1.—*Acute febrile illness suggesting meningitis followed two years later by hypertrophic osteo-arthropathy; repeated hemoptyses from varix in pharynx; primary new growth of the lungs with metastases in internal organs and right femur; autopsy.*

D. J. R., a man aged 32, entered the Boston City Hospital, March 9, 1909, service Dr. George G. Sears.

*Personal History.*—Until his acute illness three years ago, the patient has always been in perfect general health. Venereal diseases denied. Smoked moderately all his life and as a rule has taken from two to six glasses of beer daily, but very rarely any stronger beverages.

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* The Roentgen-ray studies were largely made in the Roentgen-ray Department of the Boston City Hospital under the direction of Dr. Francis H. Williams, to whom I am deeply indebted for constant cooperation and advice. My thanks are also due Dr. Walter Dodd of the Massachusetts General Hospital, and Dr. George H. Holmes of the Long Island Hospital, for the examinations made of the cases from those institutions.

The patient's occupation is that of a foundryman and most of the time he works in front of an oven, which work requires him to open the oven frequently, when he is exposed to very intense heat and gases. He is also often obliged to handle the molten metal when it is poured into the mold. At short intervals he goes outside for sand and other materials, and this, during the colder months of the year, necessitates frequent abrupt changes from an excessively hot atmosphere to a very cold one. He states that the vapors from the furnaces not infrequently produce uncomfortable symptoms and at such times he is accustomed to go to the door or window for air. It is not uncommon for workmen in the foundry to be overcome with the heat and gases, especially during the winter months when the ventilation is bad. The victim becomes very pale and usually unconscious, but never exhibits spasms or convulsions. The attacks, as a rule, last but a few minutes, the workman when taken into the fresh air recovering promptly.

About three years ago when on the street, he was suddenly seized with an intense stabbing pain at the base of the skull. By the time he reached home the pain had become agonizing in character and when attempting to untie his shoes, he fell to the floor unconscious. He was confined to bed for three or four months. He states that during most of this period he had a temperature ranging from 101 to 104 F. and much of the time was delirious. The pain which he suffered is described as very intense, constant and boring, confined to a small area in the midline just below the occiput. The head, he said, "felt as though it weighed a ton." The symptoms were somewhat relieved when in a prone position, but on standing or sitting he had the sensation as if the head were resting on sharp spikes, any movement of the head causing it to jostle on these points. There was no retraction of the head, but on account of the pain, motion in the cervical portion of the spine was extremely limited. Many drugs were administered but none gave him the slightest relief from the pain. There were no other special symptoms which he can recall. Convalescence, though protracted, seems to have been complete and after ten months from the onset of the symptoms he went back to his old work where he remained until four months ago. During this period he was in excellent general health and weighed 180 pounds, or more than at any previous time.

During the past four months he has worked in a car barn, being on night duty. His hours were somewhat irregular and his sleep, in consequence, much broken. The building was damp and his work necessitated much exposure during bad weather. He did not feel so well and lost considerably in weight. Up to this time there have never been any respiratory symptoms, the digestion has been good, and the bowels regular.

In spite of his statement that he has been in excellent general health since his recovery from the illness noted above, he gives the history that about a year ago he first experienced pain in the instep which made it very difficult for him to walk about. This symptom was especially noted at night after being on his feet all day. A diagnosis of flat foot was made, but plates gave no relief. Some months later he had pain in the knees also and these joints were very much swollen and tender, but not red. He still remained at work. The joint symptoms have shown a great variation in intensity, but on the whole have become progressively worse. When lying down or sitting comfortably in a chair, there is practically no discomfort, but when walking or standing the joints above mentioned as well as the spine are stiff and motion is painful. After being in a sitting position for some time, he finds it extremely difficult to straighten up and says he feels afraid that the back or knees will give out. He attributes the exacerbations largely to fatigue and changes in the weather. At present the joints are more troublesome than ever. He finds it impossible to keep them in one position for more than fifteen or twenty minutes. He says when moving about he can sometimes feel the fluid shaking in the knees. Of late the hands and wrists have become much swollen. In the case of all the joints the symptoms which were so variable at first have lately become remarkably constant in

character and the pain is much less severe. A symptom which is now much more troublesome than the pain is a sensation as though the skin over nearly all the joints were under great tension. The back is rigid and torsion of the cervical spine, which is limited, causes a creaking sound and a grating sensation.

The patient had never noted any clubbing of the fingers until his attention was called to the condition and he is entirely unconscious of other changes in the arms or legs apart from those described as affecting the joints.

*Physical Examination.* The patient is a well developed but poorly nourished man, slightly pale and very nervous. The degree of emaciation is rather extreme, the paniculus adiposus having almost entirely disappeared. All the skeletal muscles present a considerable degree of atrophy but this change is most evident in the interossei of the hands. His teeth are neglected, many with cavities. Except for a considerable degree of pallor and excessive perspiration, the

Fig. 1.—(Case 1.) Clubbing of toes and characteristic deformities in joints and lower legs.

skin is normal. The mucous membrane of the throat is slightly pale and shows an atrophic condition. In the inner side of each cheek near the angle of the mouth a few pigmented areas are noted. The lymph-glands are normal. The nipples are enormously increased in size, deeply pigmented and slightly sensitive. The features are unchanged except that the nose is a trifle bulbous.

The appearance of this patient, especially when standing or walking, is very striking, indeed. The trunk is sharply flexed on the thigh and carried very stiffly, the spine seemingly absolutely rigid. The gait is very stiff, clumsy and slow. He gets up and down with the greatest difficulty and finds it almost impossible to climb stairs.

Examination of the spine shows that the normal dorsal and lumbar curves are nearly obliterated and motion in any direction is practically *nil*, except in

the cervical portion, where mobility is still preserved to a moderate degree. Rotation of the head is accompanied by a slight grinding or creaking sound which is readily audible. Any attempt at motion in the dorsal or lumbar spine produces considerable pain. In spite of these changes noted in the spine, no gross changes in the vertebrae are evident. No abnormalities could be made out in the bones of the head. Considering the fact that the patient is a man of large frame, the bones of the shoulder girdle, trunk and pelvis are not considered to be increased in size.

Alteration in the hands, arms, feet and legs are quite extraordinary. Both the hands and feet, but especially the former, are very gross and approach the condition of gigantism. The ends of all the digits are enormously clubbed, the changes involving the whole distal phalanx. The two diameters are almost equal and the clubbed ends are, in consequence, practically globular. Although it is evident that the thickening is largely due to changes in the soft parts, palpation indicates that there is also some bone enlargement. The nails are perhaps a little thickened and the longitudinal ridges augmented, but the most striking change consists in a marked accentuation of the normal curves. The nail-beds are not particularly injected. There is considerable cyanosis. All the joints of the hand are enlarged, slightly tender, and moderately painful with motion, but without any evidence of increase in surface temperature or redness. The changes appear to be largely due to increase in the periarticular soft parts and there is no obvious hydrops articulae. The muscles of the hands, and especially the interossei, are considerably atrophied. Changes of a similar nature but of lesser degree are noted in the joints of the feet. The forearms and wrists are grossly abnormal, the usual tapering form having entirely disappeared. The diameter of the forearm, in other words, appears uniform throughout. The radii and ulnae are clearly enlarged, the surface feeling smooth and regular. There is likewise considerable thickening in the soft parts but no clearly marked edema. The wrists are enormous and present the same appearances as above described in the smaller joints of the hand, except that there is possibly some increase in the joint fluid and the pain with motion is much more marked. The elbow joints also show moderate changes of this same general type. In a general way the changes described in the forearms also pertain to the lower legs, the portions from the knees to the ankles being practically cylindrical. In the lower half, especially, the tibiae and fibulae are easily felt as enormously enlarged throughout. Fairly acute tenderness with firm pressure over the bones. The ankle joints are greatly swollen, apparently contain a considerable amount of fluid and are slightly tender and painful with motion. No other signs of inflammation. Similar changes are present in the knees, but here the bony parts feel very massive. Motion is much restricted.

The lungs, heart and abdominal organs seem normal.

Temperature normal. Examination of the urine gives no evidence of any disease of the genito-urinary tract.

The subsequent history of the patient is interesting, chiefly with reference to the frequent remissions and exacerbations of the disease. In the summer of 1909 the patient was sent to the country for a month's vacation and returned very much improved in general condition and especially with reference to the symptoms in the joints of the legs and arms. The swelling had largely disappeared, the joints were much more supple, there was no longer any pain and only insignificant sensitiveness in the joints with motion. The forearms and lower legs appeared much less massive and even the clubbing in the fingers had slightly diminished. The patient stated that he felt in excellent general condition. Soon after his return he went to work running an elevator and continued at this occupation for nearly three years. During this period he had several sharp exacerbations, with a return of the symptoms in the arms and legs from which he previously suffered. During these exacerbations he suffered also from constitutional symptoms, feeling marked malaise and weakness,

anorexia, insomnia, etc. He was also subject at these periods to excessive sweating, especially at night, and to frequent chills.

In September, 1910, he began to be troubled with a very persistent hacking cough and several times raised blood. When lying on the right side he frequently suffered from a severe choking sensation. At such times he would frequently cough up a considerable amount of fresh blood. The temperature was always found normal. The sputum did not show the presence of tubercle bacilli and no abnormal signs were found in the lungs. Roentgen-ray examination gave no indication of any changes in these organs. A tuberculin test was negative. An examination of the throat by Dr. Leland revealed the presence of an enormous varix behind the epiglottis, which was evidently the source of the hemorrhages. Treatment of this condition gave entire relief from hemorrhages for nearly a year.

Fig. 2.—(Case 2.) Clubbing of fingers and toes. Typical deformities in forearms, lower legs, wrists and ankles.

In the fall of 1912 the patient was finally obliged to give up his work permanently and from that time on the course of the disease was steadily progressive. The symptoms in the legs and arms remained about the same but he became gradually weaker and found it more and more difficult to get about. He was excessively nervous, much depressed and at times showed symptoms of insanity. He frequently showed symptoms of cardiac weakness and examination gave signs of mitral insufficiency and dilatation. He also developed a very extreme and persistent blepharitis.

His condition finally became so critical that in September, 1913, he was again sent to the Boston City Hospital. For the first time definite signs were found in the lungs. There was slight dulness at the right apex, to the spine of the scapula behind and to the third rib in front. Over this area the breathing was

moderately bronchovesicular in type and the fremitus definitely increased. No râles. A Roentgen-ray examination showed a fairly dense shadow corresponding to this area of dulness, but no other changes in the lungs. There were no pulmonary symptoms. A diagnosis of pulmonary tuberculosis was made and the patient referred to the Boston Consumptives' Hospital, where he died Dec. 10, 1913.

*Roentgen-Ray Examination March 11, 1909.*—The entire skeleton was examined at this time and at regular intervals until the patient's death, Dec. 10, 1913. Considering the relatively slow development of bone changes in general, it was thus possible to study the progress of the disease in the osseous system for a period of nearly five years. In the history above, attention was called to the extraordinary exacerbations and remissions which took place from time to time in the clinical course of the disease. Considering its distribution and its severity, it is not surprising that we fail to find any definite evidence of bony absorption coincident with the periods of remission. Although for considerable periods bony changes seemed to be at a standstill or progressed only slowly, the general course over the period of five years was one of more or less irregular progression and the contrast between the appearances in the bones at the time of the first and last examination is very striking.

March 11, 1909, the Roentgen-ray examination gave the following: Nearly the entire skeleton shows to a greater or lesser degree alterations in the bones characteristic of hypertrophic osteo-arthropathy but are most marked, as is usually the case, in the long bones of the forearms and lower legs, the phalanges of the feet and hands, and the carpus and tarsus.

The essential bony changes consist in a subperiosteal formation of new bone, the original osseous tissue appearing normal and the two everywhere distinctly differentiated.

The distal phalanges in both the feet and hands show a general burr-like proliferation in their outer portion. All the bones of the metacarpus and metatarsus show alterations which consist in an even layer of new bone throughout the diaphysis, varying in thickness from one sixteenth to one-eighth of an inch in the case of the first metatarsal bone. In a few instances there is an irregular, cauliflower-like proliferation over the epiphyseal part. Similar changes are also seen in the first row of phalanges in both the hands and feet, but of much less degree than in those just inside. In several at about the level of the outer and middle third, the lateral ridges which form the attachment for the flexor tendons show a relatively immense proliferation. In the middle row of phalanges proliferation is noted only occasionally and the distal phalanges are unchanged except in their outer half.

The tarsus and carpus participate in the changes to a rather slight degree. The os calcis in either foot gives no evidences of abnormalities, except that in the lower half of the posterior portion there is a considerable degree of formation of new bone, continuing down into the tuberosities, which are considerably increased in size. The radii and ulnae of both forearms are immensely altered, the subperiosteal layer of new bone being present throughout their entire length, but thickest about an inch above their distal extremity and gradually diminishing in thickness toward the elbow joint. In the case of both bones, the greatest deposit is on the outer side. In the case of both radii for an extent of about two inches at their distal ends, there is an immense deposit of irregular new bone which extends to the joint line. A similar picture is seen in the bones of the lower legs. A thin shell of new bone is readily made out in the lower third to one-half of the humeri, also in the outer half of the clavicles and the acromion processes. The bones of the head and the ribs seem normal. In contrast to the humeri, the femora are changed throughout their entire length and to a considerably greater degree, but much less, however, than the bones of the lower legs. The patellae are considerably changed in their nonarticular portion. Characteristic osseous changes are shown along the crests

of the ilia, but otherwise the pelvis is normal. No definite bony proliferations can be made out in the spine.

The joints are everywhere surprisingly free, there being no evidence of changes in the joint cartilages. In the ankles, knees, wrists, elbows and several of the joints of the hands and feet, the irregular proliferation of bone in the epiphyseal portion of the bones forming the joints stops abruptly at the edge of the cartilage.

Subsequent roentgenograms show the successive stages in the process of bone proliferation just described. In the bones most involved the sharp line of demarcation between the old cortex and the new subperiosteal layer gradually disappears and finally in the bones of the lower legs is almost nowhere to be

Fig. 3.—(Case 37.) Marked clubbing but no enlargement of forearms and lower legs. Roentgen-ray shows slight formation of new bone in the tibiae.

made out. The outline of the long bone is in many places quite smooth and regular, but in others is very much broken and uneven. Small cysts, varying from one-half to one centimeter in length, are in several places to be made out. In contrast to the appearances shown in the early roentgenograms, the later ones show a very great decrease in the density of the original bony shaft. The entire structure is apparently altered, the marrow space is completely obliterated and the normal texture of the bones replaced by a shadow which is very thin and of extremely variable and irregular density, somewhat resembling the appearances seen in advanced osteitis deformans. Even in the roentgenograms taken but a few months before death, the joints are still seen to be free, although the changes immediately adjacent, described above, are greatly augmented.

*Necropsy* No. 170, Dec. 10, 1913, by Dr. J. Earle Ashe.

*Anatomical Diagnosis.—Periostitis ossificans; primary carcinoma of the right lung with metastasis in right femur, left kidney, brain, and left lung; chronic adhesive pleuritis; chronic bronchitis; moderate chronic fibrous mitral valvulitis; early coronary sclerosis; spleen, chronic tumor; moderately fatty liver; moderate chronic interstitial nephritis; moderate hydrops and multiple yellow softenings from emboli in the brain; visceroptosis; chronic blepharitis.*

Body: Moderately emaciated. Pupils are equal, regular, 5 mm. in diameter. The palpebral conjunctiva is congested, the edges of the lids, especially the lower, are much thickened and excoriated and there is a small amount of thick, yellow, purulent material in the right outer canthus. The ears are rather prominent, the teeth well preserved and the palatal arch rather high. The tongue and jaws show no enlargement. Patches of yellow, superficial, dry, bran-like scales over upper chest and lower abdomen. The breasts are a trifle more prominent than usual. External genitals normal. None of the superficial lymph-nodes are enlarged except the epitrochlear, which are readily palpable. The radial arteries are stiff and tortuous.

There is some irregular thickening of the lower ends of both humeri, though the shafts are apparently free. On the radii and ulnae, however, can be felt distinct irregular thickenings, more marked on the lower ends of the former, though the shafts are distinctly involved. The finger ends are markedly clubbed, apparently due chiefly to enlargement of the soft parts. The nails are of the typical "Uhrglassform" and the free edges are widely separated from the fingers by a thick matrix. They are a little thick, but not hard or dry. No alteration of the carpal or metacarpal bones can be detected. The thighs are partially flexed on the abdomen, the legs likewise on the thighs. In both cases it is impossible to overcome these contractures. The lower ends of the femurs are greatly thickened by irregular bony masses. Just above the inner tuberosity of the right femur is a distinct mass which as felt through the skin is rather soft and contains particles of bone. The right knee joint was exposed and found moist and contained fairly firm black blood clot, slightly adherent to the articular surfaces of the condyles. There are several small superficial erosions of the articular surfaces of the right condyle of the femur, external tuberosity of the tibia and outer facet of the patella. There is a small, fairly sharp exostosis springing from the base of the tibial spine. The tumor felt through the skin is 6 cm. long by 3 cm. wide and 3 cm. in thickness. It is covered by thick periosteum and the outer two-thirds is firmly fibrous and contains cancellated bone. The inner portion is soft, lobate, and of a brownish-red color and the adjacent portion of the shaft under the tumor is eroded to conform to its shape, and so deeply in the lower portion that the inner condyle is practically a shell. About the tumor there is a considerable amount of loosely clotted blood. The tumor does not seem to be attached to the bone except by the periosteum and can be shelled out of its nest in the bone without difficulty, leaving an area of porous exposed bone, which is apparently not infiltrated by the tumor.

The femur was exposed for its lower half. It is enormously thickened — posteriorly by long stalactite-like exostoses — longer and thicker over the tuberosities, and all pointing upward. The remainder of the surface is made up of fairly uniform plaques of subperiosteal bone, which are thicker toward the lower end. The periosteum is somewhat thickened; the new bone is very firm and cannot be separated from the original shaft. The fibulae are both much enlarged, the lower two-thirds being almost as thick as the tibiae. They are rather rough and irregular as palpated through the skin, while the tibiae are comparatively smooth. The left tibia was exposed at about its middle. The periosteum was found moderately thickened, beneath which flat plaques of new dense bone had been laid down. The cortex beneath this is hard, averaging about 1 cm. in thickness. Beneath this again is a thick layer of cancellated bone enclosing yellow, apparently unaltered, marrow.

The right leg from the middle down and including the foot is swollen and pits on pressure, edema being due to pressure on the femoral vein by the tumor in the region of the knee. The skin of the soles of the feet and under surfaces of toes is thick, rough, and of a light brown color. There is distinct clubbing of the toes with bowing of the nails. The second toe of the right foot incised on under surface and enlargement found to be due chiefly to thickening of the soft parts. The distal phalanx was excised and found to be much broader than normal at its tip.

Head: External occipital protuberance is palpable, but not enlarged. The hair is thick. The scalp strips fairly easily. Calvarium is not thickened but the bone is somewhat more dense than usual due to the fact that the diploe are not quite so prominent as usual. Skull averages 0.5 cm. in thickness. The dura is free from the calvarium and from the underlying membranes, except

Fig. 4.—(Case 39.) Marked clubbing, but only suggestive thickening in the lower leg. Roentgen-ray reveals rather general bony proliferation.

along the longitudinal fissure, where Pacchionian bodies penetrate. There is some edema of the subarachnoid space over the upper surfaces of the frontal lobes. The pia and arachnoid are otherwise free. The vessels are well filled, particularly those of the vertex and show no sclerosis. The posterior end of the left internal orbital convolution is adherent to the orbital plate of the frontal bone for an area of 1 cm. in diameter. When these adhesions are broken the cortical tissue immediately beneath is soft and white with small yellow mottled areas. In the posterior portions of the middle frontal convolutions on both sides are areas of similar cortical softening with the yellow mottling. In posterior portions of the upper frontal on the left side is a soft area, but more gray and without the yellow color. These areas are all practically the same

size, i. e., from 1 to 1.5 cm. in diameter. The ventricles and appendyma are free.

The pituitary body is readily removed from its position, measures 14 by 6 mm. and is of usual consistency. On section, however, it is darker than normal, apparently from the presence of blood. There is found to be some exaggeration of the sinus markings in the lower fossa of the skull, particularly the left lateral sinus, which is almost entirely surrounded by bone. The crista galli is much more prominent than usual, extending into the falx for 1.5 cm. and the anterior portion of the occipital bone bulges posteriorly quite perceptibly, though not enough to compromise the medulla. The bony air sinuses are not enlarged and are free from exudate.

On section a number of small areas of cortical softening are disclosed aside from the ones already described.

1. Left middle occipital, 0.5 cm.
2. Posterior tip of hippocampal 1 cm.
3. Left ascending parietal, 0.5 cm.
4. Upper surface, right gyrus fornicatus, about the middle, 1.5 cm.
5. Right lenticular nucleus, about the middle, 1 cm. in diameter running practicallly the whole length and involving a small portion of middle of internal capsule.
6. Lower end of the ascending frontal and parietal convolutions that cover in the Island of Reil, and extending into the contiguous cortex of the Island, 1.5 cm. in diameter and 2 cm. long.
7. Left marginal convolution, lower edge, 1 cm. in diameter.
8. In tegmentum of the pons.

These foci are all in the state of yellow, or early light softening.

Primary Incision: The primary incision shows nothing remarkable. Costal cartilage, ribs and sternum normal. Thymus practically obliterated. Pericardial sac free.

Left Lung: Pleura at apex slightly thickened and adherent, at which point the parenchyma is thickened also. In lower lobe three small masses 1 to 2 cm. in diameter, circumscribed, hard and cut surface whitish with reddish brown center. Vessels and bronchi free.

Right Lung: Pleura densely adherent over posterior portion of upper and adjacent upper one-quarter of lower lobes. Parenchyma crepitant throughout middle lobe and in anterior half of upper and all but upper portion of lower. The remainder is uniformly infiltrated. On section these infiltrated areas appear grayish-white with small yellow mottling and of firm consistency. This tissue is continuous in the two lobes through the interlobular pleura. The tissue behind this indurated parenchyma is red, necrotic, rather pultaceous, and largely ulcerated away to form a very irregular cavity in both lobes. The walls are granular but show no fibrosis. The overlying pleura is infiltrated but the ribs do not seem to be involved.

Heart: Moderate fibrosis of mitral valves.

Spleen: Enlarged, 320 grams. Capsule smooth and tense; consistency increased.

Stomach, intestines, pancreas and suprarenals appear normal.

Liver: Slightly enlarged and edge rounded. On section the central zones are dark and somewhat depressed, the peripheral areas of the lobules are of a yellowish tint.

Kidneys: Moderate interstitial changes. On the anterior surface toward the upper pole of the left is a slightly elevated white nodule 2 cm. in diameter. On section it is found to be 8 cm. deep and the cut surface is white, with bright yellow mottlings.

*Microscopic Diagnosis.—Primary carcinoma of lung (right from bronchial mucosa), metastasis to left lung, left kidney, periosteum of right femur, lymph-gland right knee, multiple to brain; ossifying periostitis; chronic splenic tra-*

Fig. 5.—Roentgenogram of left hand (Case 1) showing characteristic subperiosteal new bone encasing the shaft of the ulna and radius. Note the involvement of the epiphysis. Nearly all of the metacarpals and first row of phalanges present irregular deposits along the diaphyses. Slight proliferation is evident in the distal phalanges.

*beculitis and capsulitis. Heart: Cloudy swelling; focal chronic interstitial myocarditis. Liver: Chronic passive congestion; moderately fatty. Suprarenal: Congestion. Kidney: Moderate chronic interstitial and capsular nephropathy. Pituitary: Hyperplasia. Soft parts of fingers and toes — obstructive distention of sweat ducts; some hyperplasia.*

*Microscopic Examination.*—Brain: Sections from four of the areas of cortical softening show identical features. The center is necrotic and surrounded by tumor cells which in type and arrangement conform closely to those of the parent tumor. Considerable glial hyperplasia in surrounding brain tissue.

Spleen: Capsule, trabeculae and artery walls moderately thickened.

Heart: Some cloudy swelling and focal areas of fibrosis.

Liver: Moderate central congestion and some fatty infiltration in the peripheral cells.

Adrenals: Marked congestion; considerable vacuolization of cortical cells.

Kidney: Changes largely interstitial and of only moderate type. The tumor metastasis consists of dense connective tissue enmeshing adenomatous mass of tumor cells. The renal tissue is invaded.

Pancreas: Slight fatty infiltration.

Pituitary: Moderate increase in number of gland cells with very little hyalin substance in acinar spaces.

Lungs: In the infiltrated areas the alveolar tissue is entirely displaced by the tumor, which consists of columnar epithelium supported by a vascular young connective tissue stroma and forming irregular alveola-like spaces. In some areas these spaces are filled with tumor cells unattached to the lining cells and much more irregular in size and outline, though distinctly epithelial in type. The nuclei vary greatly in size and shape and many show mitotic figures. No cilia are found. A few spaces are lined with young, regular cuboidal cells such as are seen in the fibrosed lungs, and which show only slight evidence of malignant characteristics. In the tumor cells crowded in the spaces there is a tendency to metamorphosis to the squamous type. The tumor is essentially cellular, but in a few small areas the connective tissue stroma is increased and shows hyalin. Several areas of necrosis and some hemorrhage are seen along the edge of the tumor. Rarely there is evidence of slight inflammatory reaction. Sections from various areas of the tumor and the nodule in the left lung present identical characteristics.

Tumor at Right Knee (Fibrous Cortex): Adenomatous groups of cuboidal cells surrounded by abundant young connective tissue. Several areas of necrosis, involving both connective tissue and tumor cells. The inner, softer portion is more cellular, the squamous type predominating and of the general arrangement seen in the primary growth in the lungs.

Lymph-Gland at Knee: Lymph tissue entirely replaced by connective tissue in which are imbedded irregular masses of squamous tumor cells closely packed. Small amount of surrounding hemorrhage.

Finger: From dorsum, at root of nail, rather thick layer of cornified epidermis. Some edema of cutis and arterial walls are thickened.

Eroded bone at site of periosteal metastasis. Very active osteoclastic bone destruction of cancellated tissue, at the same time there is new bone being developed on the trabeculae by osteoblasts. Some hemorrhage into marrow spaces. Small groups of tumor cells, showing acinar arrangement, usually, are in the marrow spaces nearest the surface.

Toe: Soft tissue from ball. Thick layer of cornified epidermis. Papillary layer markedly indented. The striking feature is the dilatation of the sweat-ducts. They are tortuous and can be followed into epidermis where an occasional cross section shows lumen occluded by hyalin material.

Terminal Phalanx of Toe: Loose cancellated bone, with distinct hypertrophy of sides, where narrow spaces are filled with loose, young connective

tissue containing stellate cells and a thick layer of elongated cells (osteoblasts) are laid down on the bone trabeculae.

Femur: New subperiosteal bone, much looser than normal cortical bone. Osteoplastic bone formation is still going on. No osteoclasts. Most of the marrow spaces contain fat and the usual marrow cells. Others are plugged with small particles of disarranged bone trabeculae enmeshed in a mass of partially necrotic cellulo-fibrillar material.

Tibia: Subperiosteal new bone, cross section. Wide Harvesian spaces contain fat and marrow cells in some instances, in others a loose young connective tissue containing stellate cells. On longitudinal section the subperiosteal line is rather irregular from active lacunar resorption. Masses of osteoblasts on under surface of periosteum particularly over points of osteoclastic activity. Some of the marrow spaces contain necrotic bone as described in other section. Medulla not remarkable.

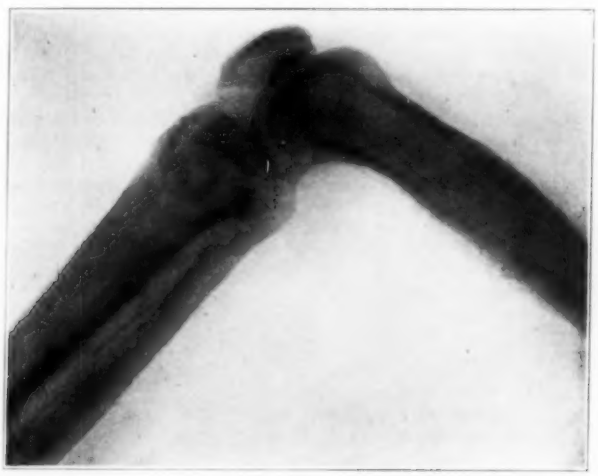

Fig. 6.—Roentgenogram of right leg (Case 1). In the femur the layer of new bone is sharply marked off from the old shaft which remains essentially unchanged. The epiphysis is free. The tibia and fibula are altered throughout and retain very little of the normal Roentgen-ray appearance. The line of demarcation between the old and new bone is not present. Both bones show uniform alterations in the epiphysis as well as the diaphysis, but the knee joint is only slightly involved. The patella is correspondingly altered.

Marrow (Tibia): Rather richly vascular fatty tissue containing a few spicules of bone and very few cells, the latter about the blood vessels. These cells are mostly mononuclear though there are a few polynuclear cells and several megalokariocytes.

CASE 2.—*Pleurisy with effusion; chronic pulmonary tuberculosis with extensive cavity formations; tuberculous enteritis; mitral regurgitation and stenosis; pulmonary hypertrophic osteo-arthropathy.*

E. M., aged 30, entered the Boston Consumptives' Hospital July 10, 1908.

*Personal History.*—Until the onset of the present illness the patient enjoyed excellent general health. Venereal diseases denied. Habits good except for excessive cigarette smoking.

About four years before entrance he had a severe attack of pleurisy with effusion and was tapped. The convalescence was very slow and he has never regained his former good health. He was examined at that time at the Boston Dispensary and no signs of pulmonary tuberculosis were found. About a year later he had another severe attack of pleurisy and a diagnosis of pulmonary tuberculosis was then made. He was sent to the State Sanatorium at Rutland, Mass., where he remained for about six months, improving greatly in general health.

Since the first attack of pleurisy, he has had nearly constant cough, which has become increasingly severe in character, and has lost much in strength and weight. The sputum, which was at first scanty, has become more and more purulent, at times has contained blood and is frequently very foul. There is severe dyspnea with exertion. About three years ago he was troubled for some time with severe night-sweats, but since then has had none. There have been no gastric or urinary symptoms, no edema.

The patient noted at the time of the first attack of pleurisy that the ends of the fingers were slightly larger than normal and he is positive that he has observed a gradual increase in this condition from year to year. He is quite as positive that there were never any changes in the forearms or lower legs until within the last six months, since which time there has been a definite increase in the size. No pains whatsoever are experienced in either the forearms or lower legs, but the bones are exceedingly sensitive to pressure and if injured slightly are sore for some days.

*Physical Examination.*—The patient presents a typical picture of advanced consumption. He is excessively weak, dyspneic with the slightest exertion, coughs frequently and raises an abundant, rather foul, greenish-yellow sputum.

The heart presents the classical signs of mitral regurgitation. There is an extensive bilateral process in the lungs, with signs of softening which are more marked on the right (tuberculosis).

Abdominal examination negative. Reflexes normal.

The arms distal to the elbow joints and the legs below the knee joints present a most striking condition. The forearms look massive and the normal proportions are very much altered, the forearm above the wrist being much enlarged so that it seems almost cylindrical, the lower portion being hardly less in diameter than the upper. There seems to be no definite edema but the soft parts feel thickened. More particularly, the bones are felt to be distinctly enlarged, the surface smooth and tender to deep pressure. The hands appear in general rather massive, but without edema. The most striking thing is the rather extraordinary clubbing of the ends of all the fingers, the thumb showing the most exaggerated form. The nails are much thickened and show an accentuation of both curves — the "parrot-beak" type. Moderate cyanosis of the nails. The nail bed is raised and definitely hyperemic. The wrists and ankles are greatly swollen and stiff and motion is moderately painful, yet there is no redness or increase in the surface temperature. The knees are less affected. The lower legs and feet present changes exactly analogous to those described in the hands and forearms though perhaps slightly more marked. Clubbing in the great toes is distinctly more than in any others.

Sputum greenish-yellow, mucopurulent, moderately fetid in odor. Large number of bacteria with many typical tubercle bacilli, single and in clumps. Urine examination negative.

The patient remained in the hospital until April 22, 1909, and improved very satisfactorily in general condition although the process was not considered arrested. At this time he left against advice to go back to work. Since then he has been frequently readmitted but on the whole has steadily lost ground.

April 24, 1910 Patient's general condition is distinctly worse than at entrance in 1908. The process in the lungs has advanced strikingly. The left lung shows marked signs throughout and evidences of a large cavity in the

midscapular region behind and from the second to fifth rib in front. The heart is displaced to the left to such a degree that the right border is about 2 cm. to the left of the left sternal border.

The condition in the limbs described above is more striking than ever.

Fig. 7.—Roentgenogram of right ankle (Case 1) taken March 11, 1909. Note the sheath of new bone surrounding the lower end of the tibia as far as the epiphysis, the fibula throughout, the shaft of the metatarsals and the proliferation along the outer edge of the os calcis and the cortex of the bones of the tarsus.

Roentgenograms of the entire skeleton made at this time show the following: The phalanges of the left hand present no abnormalities, unless it be a slight proliferation in a few of the distal ones. All the metacarpal bones, however, show a distinct thin layer outside the shaft, involving the bone throughout its entire length. The deformity is greatest in the metacarpal bones of

the thumb and little finger. The process seems to be confined entirely to the shaft of the bone in each case. There are no definite changes in the carpus, but the lines between the individual bones are more or less obliterated. The joints throughout the hand are normal. The left radius and ulna present changes exactly similar to those described in the metacarpal bones except that the outer layer of the new bone is more irregular and variable in density. There is no change to be noted in the ends of the bones and the joints are free. In the right hand as in the left, the phalangeal bones are normal. All the metacarpal bones with the exception of the third have a definite thin layer outside the old shaft, which is most marked in the thumb and first finger. Changes of the same type and degree as in the left are noted in the right ulna and radius. The arteries do not show.

Roentgenograms of the upper arm and shoulder girdle are without evident changes in the bones. A few of the ribs, however, show a questionable deposit of subperiosteal new bone. The bones of the skull and face are normal.

The phalanges of the feet are normal, but the first, fourth, and fifth metatarsal bones show slight but definite changes of exactly the same type as noted in the metacarpal bones. The tarsus is free from changes. The tibia and fibula in both legs show an irregular, definite layer of subperiosteal bone throughout the shaft, in places nearly a quarter of an inch in thickness. These changes in places extend beyond the epiphysis nearly to the joint surface in the case of the knees. The femurs present alterations noted in the bones of the lower legs but of much less extent. Nothing definitely abnormal can be made out in the pelvis.

A year later a second series of roentgenograms was made of the entire skeleton. During the interim the patient's condition had remained about the same. The alterations from the normal in the bones as shown by the roentgenograms are similar to those described, but are considerably more marked in all the bones previously involved and several of the phalanges of the hands and feet show beginning changes. The distal phalanges in the feet are particularly noteworthy as they have increased considerably in size, showing irregular osteophytic outgrowths mainly in the outer half but also to some extent just distal to the joints.

In April, 1911, the patient was discharged from the hospital and was not readmitted until March 24, 1913, when he seemed to be in a dying condition. The general symptoms referable to the process in the lungs were much more severe, the sputum of a definitely putrid type and very abundant in amount. There was marked cyanosis, dyspnea and considerable edema of the lower legs. He was also suffering from a violent diarrhea with five to ten loose movements daily and considerable colicky pain.

After a few weeks' residence in the hospital, he began slowly to improve, which improvement continued and by March 12, 1914, when a third set of roentgenograms was made, the patient had made extraordinary improvement. He had gained enormously in weight, was up and about the grounds daily, and suffered from almost no symptoms except dyspnea with any unusual exertion. He had practically no cough, raised no sputum except a small amount in the morning. Pulse and temperature were normal. The signs in the lungs, however, did not differ materially from those previously found, except that they were much less definite of activity.

The roentgenograms are in striking contrast to those made a year and two years previously. The bones of the hand show no changes whatsoever, except that the terminal phalanges are slightly ragged and possibly a little enlarged, and several of the bones of the metacarpus seem a little massive and dense, but without any clearly defined cortical layer of new bone. The appearances in the bones of the forearms are essentially the same as previously but a little less marked and the differentiation between the old shaft and the new bone less definite; that is, to a considerable degree the new bone seems to have

Fig. 8.—Roentgenogram of right ankle (Case 1) taken June 25, 1913. Changes in the bone as evident in Fig. 7, but of more striking degree, are present, and also in the old bone throughout.

become fused with the old. The thickness ranges from one-eighth to one-quarter of an inch. The outline is somewhat irregular.

The terminal phalanges of the feet are but little if any broader and more ragged than normal. Nothing abnormal except questionable changes in a few of the metatarsal bones. The roentgenograms of the lower legs present the same general type of changes as described earlier, but there has evidently been a great retrogression in the process previously described as having taken place in the bone.

CASE 3.—*Syphilis at 36; chronic alcoholism; cirrhosis of the liver; chronic pulmonary tuberculosis, with cavity; pulmonary hypertrophic osteo-arthropathy of acute febrile type.*

T. F. D., aged 54, entered the Boston Consumptives' Hospital Dec. 2, 1909.

*Personal History.*—In early years had measles, scarlet fever and pertussis. Typhoid fever in 1889. Seventeen years ago a severe attack of influenza. For many years a very hard drinker and a man of generally dissolute habits. Gonorrhea fifteen times and on several occasions chancroids and buboes. Eighteen years ago he had a chancre followed by secondary eruption which was untreated, but since then he has had no further symptoms of syphilis. April 27, 1905, he entered the Massachusetts General Hospital for severe hematemesis. His condition at that time was diagnosed as cirrhosis of the liver and chronic alcoholism. Somewhat later he developed paralysis of the vocal cords together with some symptoms of pressure in the mediastinum and a roentgenogram showed a slight dilatation of the arch of the aorta. In September, 1909, he again entered the hospital with an infected tarsal cyst. Following operation he had an open wound for a long period, with considerable discharge of pus. This wound was not finally healed until a secondary operation was done nearly a year later.

November 12, 1909, the patient entered the Boston City Hospital with pulmonary symptoms and there a diagnosis of pulmonary tuberculosis was made. Tubercle bacilli were found in the sputum in large numbers.

At entrance to the Boston Consumptives' Hospital the patient gave a history of a hemorrhage from the lungs about seven years previously. Since this time he has had a nearly constant cough, as a rule loose in character, but with a variable amount of sputum. For a considerable period he had had severe gastric symptoms and marked dyspnea with exertion. There has been considerable loss of strength and a decrease in weight from 185 pounds six years previously to 150. No fever, chills or night-sweats.

*Physical Examination.*—This is negative except for signs of a fibroid phthisis involving nearly the whole of the right lung and the left above the third rib, and a much enlarged liver with hard, irregular edge.

The fingers and toes show a moderate clubbing of the characteristic type, but no abnormal signs in the long bones are made out. Temperature 98 F., pulse 70, respirations 20. Urine negative. Sputum shows the presence of many tubercle bacilli.

About a month after entrance the patient began to complain of pain and stiffness of the lower spine. Shortly afterwards the left knee and leg became swollen, also both forearms, wrists and hands. The signs in the lower legs and arms, however, were not so much in the region of the joints as in the long bones. The chief symptom was a dull, constant pain which was described as deep in the bones. The forearms and lower legs were clearly enlarged, not reddened but with excessive tenderness over the bones, which felt definitely increased in size. The ankles, knees, wrists and some of the finger joints were enlarged and slightly stiff but without signs of inflammation. In spite of rest in bed and careful treatment the condition of the patient remained unchanged for several weeks, when very slow improvement took place. After several months, however, the forearms and lower legs looked less massive but the bones still felt larger than normal. This improvement in the acute condition in the

forearms, hands, feet and legs described above followed a marked improvement in the pulmonary condition. The pulmonary symptoms practically all disappeared, the temperature came down to normal and the physical signs in the lungs decreased strikingly in intensity and extent.

Unfortunately it was not possible to examine the patient with the Roentgen ray until May 7, 1910, at which time he was ready to be discharged from the hospital as an arrested case. He had gained about 50 pounds in weight and all symptoms, both of the disease in the lungs and in the limbs had entirely disappeared. The signs in the lungs had diminished materially. He had a slight dulness at both apices with bronchovesicular respiration, moderate increase in fremitus and a few scattered râles. Over a small area in the right front at the level of the second rib, distinct amphoric breathing, with slight egophony, were heard.

Fig. 9.—Roentgenogram of hands (Case 4), designed to illustrate the type of proliferation in the distal portion of the ungual phalanges seen in hypertrophic osteo-arthropathy. The remaining bones show only slight indications of the peripheral new bone present some years previously.

Forearms and lower legs still appeared more cylindrical and slightly larger than normal, but otherwise nothing abnormal could be made out. The clubbing of the fingers, though less, was still rather marked. Only slight cyanosis of the nails.

*Roentgen-Ray Examination.*—The terminal phalanges of the hands show marked but variable enlargements, the outlines being ragged and irregular. Many of the remaining phalanges seem to be thickened in the cortical portion of the shaft and the outline in places is ragged, but the line between the outer sheath of new bone and the old shaft is not everywhere evident. The bones of the feet show less marked changes. The bones of the forearms and lower legs are thickened but do not show anywhere a well marked layer of new bone. The cortex is much thicker than normal, slightly irregular in outline, and in many places gives the impression definitely of the fusion to a greater or less

degree of newly formed subperiosteal bone with the old cortex as seen in other cases. The arteries of the legs and forearms are clearly seen as tortuous, calcified lines. There is a definite though thin layer of new bone along the lower edge of the ilia and to some degree in the upper half of the femurs.

The appearances about many of the joints are noteworthy. All of the distal joints of the fingers show a greater or lesser degree of proliferation of bone, in some instances of definite osteophytes, mostly at the proximal end of the last phalanges. The ends of the next rows of phalanges forming the joint are much misshapen and irregular but without osteophytes. In several cases the line representing the joint cartilage is much thinned and the general appearance is that seen in osteo-arthritis. The middle phalangeal joint and the metacarpal-phalangeal joint appear normal. The carpus is greatly changed. In certain places actual proliferation of the bone can be seen, but the most striking thing is the appearance of matting together of nearly all the bones. The radiocarpal joints seem free. Both elbow joints, but the left more than the right, show considerable change which consists chiefly in considerable proliferation in the olecranon process and an indefiniteness in the joint line, evidently the result of bony proliferation. Changes of the same nature, as above described in the fingers, are seen in the toes, being most marked in the distal joints, but present also in the middle phalangeal joints. Lateral roentgenograms of the ankle joints show general changes in all the bones of the tarsus. There is a more or less constant layer of new bone which stops abruptly at the joint surface. No lipping can be made out. In both knees over the outer side of the external condyle of the femur and of the upper end of the tibia the surface is much roughened and proliferated with small osteophytes, especially on the tibia.

During the next year the patient continued free from symptoms and the signs in the lungs diminished. The appearances in the limbs remained about the same. Roentgenograms made March 28, 1911, showed the same general appearances as described above, but slightly less clearly defined.

CASE 4.—*Pneumonia; empyema; bronchiectasis; pulmonary hypertrophic osteo-arthropathy.*

M. M., a foundryman, aged 43, entered the Boston City Hospital May 9, 1903.

*Personal History.*—Patient has always been rugged until the past two years. He smokes and drinks to excess but denies venereal diseases.

Two years ago he had severe pneumonia, with good convalescence and apparent cure, followed about five months ago by a second attack from which he has never fully recovered. Since then he has had almost constant, increasingly severe cough, often paroxysmal, with large amounts of greenish-white foul sputum; soreness in the left side of the chest with catchy pain on coughing; dysnea; frequent headaches and anorexia; considerable nausea and vomiting; in a word, greatly impaired general health. No chills or night sweats.

The patient is entirely unconscious of any changes in the bones and declares that he has had no symptoms there.

*Physical Examination.*—A powerfully built, robust man whose general appearance gives the impression of a severe acute illness. He is somewhat pale; there is considerable cyanosis, and dyspnea is marked even when making the slightest exertion.

There are unmistakable signs of fluid in the left chest. The heart is considerably displaced to the right but is otherwise normal. The peripheral arteries are soft and not tortuous. Pulse 110, temperature 102 F., weight 170 pounds.

The sputum is mucopurulent in character and does not show the presence of tubercle bacilli. The urine is normal.

The forearms, lower legs, feet and hands present a typical condition of hypertrophic osteo-arthropathy. The hands appear gross and clumsy, although there is no edema. The terminal digits are almost globular, diameters being

nearly equal and the nails showing an extraordinary degree of curving, with great thickening and the presence in all of prominent longitudinal ridges. The forearms and lower legs are much enlarged, giving a rather cylindrical appearance but without any tenderness over the bones, or edema. The joints nowhere show any evidence of involvement except for moderate swelling, motion being perfectly free and without pain.

Soon after the above date the patient was operated on for empyema and a large accumulation of pus found. The patient was considerably relieved as a result of the operation, but even after several months, when the wound was healed, he still suffered from almost constant cough and with frequent evacuation of a large amount of sputum of the same type as described above. He improved considerably in general health, gained in weight (204 pounds), was much less short of breath, and finally resumed his work. He was seen, however, from time to time in the out-patient department and usually had a slight rise of temperature, varying from 99.5 to 101 F. The signs in the lungs remained essentially the same.

Fig. 10.—Roentgenograms of forearms (Case 40) showing a thin, irregular layer of newly formed bone about the lowed diaphyses of the ulnae and radii.

May 6, 1914. During the past ten years the patient has been under my personal observation and at periods of six months to a year roentgenograms have been made to show changes if any taking place in the bones. He has worked constantly and improved steadily in general health. The weight has held steadily at 205 to 210 pounds. Except for the cough and dyspnea with exertion he feels that he has never been so well. The cough, though less severe than in former years, is still harassing. It is worse at night and in the early morning after rising. The sputum is small in amount, never purulent or of foul odor. The forearms are frequently painful, though never tender. Dull pains are also present about the knees at times.

On examination signs are still present in the left lower back, but of much less definite character than previously. There is still some cyanosis of the lips. In general the changes in the limbs appear to have subsided to a considerable degree.

The Roentgen-ray examination revealed much more extensive alterations in the skeleton than were evident on physical examination. The characteristic bone changes seen in hypertrophic osteo-arthropathy are present in the bones of the forearms, lower legs, lower third of humeri, and in the lower third of the femurs. The bones of the feet are more altered than are those of the hands. The distal phalanges are strikingly fanshaped, very irregular and at their proximal ends near the joint surface nearly all show a few small osteophytic growths. The second row of phalanges are but little changed, whereas the first and the metatarsal bones all show more or less subperiosteal proliferation of bone. The changes in the hand are of a similar nature, but less marked. The remaining bones of the skeleton appear unchanged.

The changes in the joints are rather striking, especially the knees, ankles, elbows and wrists. In each instance besides the evident thickening in the soft parts, there is marked proliferation of the bone immediately adjacent to the joint surface and especially in the knee there is marked lipping. In these joints the cartilage is quite irregular and in a few places almost obliterated. In the case of the elbow joints, the increase in the bone substance is certainly much greater in the ulna than in the humerus, the olecranon process being greatly augmented in size by irregular newly-formed bone throughout the greater sigmoid cavity. In the carpus on each side there is a slight appearance of matting together of certain of the bones and in a few, slight proliferation is to be made out. About the epiphyseal portion of the radius and the very border of the joint cartilage is an immense, irregular, cauliflower-like new bone formation. The joint cartilage is evidently normal. In the hands and feet, only the most distal joints are essentially altered. The principal change consists in the proliferation of adjacent parts as in the case of the large joints, but in the feet the joint cartilage also seems more or less changed.

The roentgenograms made in subsequent years show the same general changes. There is no evidence that the process has advanced and indeed in many of the bones there has been a more or less striking retrogression. The layer of subperiosteal new bone has become thinner, somewhat more dense in places, and, as a rule, less sharply marked off from the original shaft.

CASE 5.—*Pleurisy with effusion; old phthisis; asthma; arteriosclerosis; pulmonary hypertrophic osteo-arthropathy.*

Mrs. C. C., aged 48, Boston City Hospital, Out-Patient Department, No. 16320. Seen Dec. 6, 1907.

*Personal History.*—Usually in excellent general health. About twenty years ago, the patient had an attack of pleurisy in the right side, followed by a dry, hacking cough for some months. Occasional attacks of asthma since childhood, which later diminished in severity and none now except very rarely in the cold weather. Pneumonia seventeen years ago.

Since last March she has had gradually increasing dyspnea, no palpitation, slight edema of the ankles and burning, toothache-like, intermittent pains in the long bones which are worse at night, when she is fatigued, and in cold and wet weather. At first they were chiefly in the legs, lower back, and forearms, but are now confined to the upper third of the left arm and along the course of the spine between the shoulders; occasionally in the wrists and knees, with some tenderness over the site of the pains. She has noticed for the last few months increasing stiffness and clubbed deformity of the ends of the fingers, which occasionally feel cold, but never numb, and with no other disturbances of sensation. The patient has lost 25 pounds in weight during the past year.

The general health is good, but she finds that she is weak, clumsy and slow in getting about.

*Physical Examination.*—A very tall, emaciated, sallow looking woman. Skin atrophic. Lips and fingers cyanotic. The face appears gross and somewhat mask-like, somewhat suggestive of acromegaly. Pupils react normally. No glandular enlargement.

Chest: Left clavicle more prominent than right; right side of chest seems to move less with respiration than left. Apical outline on right considerably diminished, and whole right side dull, becoming flat below the third rib front and a point two inches above the inferior angle of the scapula behind. In the upper part of the right chest the respiration is faint and of vesicular character; over the lower part, practically absent. Fremitus is normal above, but absent over lower part of right chest.

Heart: Normal in position. Left border just outside left nipple line. Impulse felt in sixth space. Sounds clear, rather sharp. No murmurs heard. Aortic second sounds somewhat accentuated. Pulse regular, rather full volume and high tension. Arteries tortuous and palpable.

Abdomen negative.

The bones of the lower legs and forearms in their lower third feel slightly enlarged and the parts appear definitely massive. No tenderness. Slight edema of the ankles. Knees somewhat swollen, evident thickening of the soft parts, and bony structures also feel massive; signs of small amount of fluid; motion normal; no redness or tenderness. Fingers and toes clubbed and of characteristic type.

No tubercle bacilli found in the sputum. Temperature 99.4 F. Urine normal.

*Roentgen-Ray Examination.*—All the distal phalanges of the hands and feet are more or less changed, in some instances rather strikingly. Several of the first row of phalanges show slight characteristic changes. In the metatarsus and metacarpus all the bones show a varying degree of subperiosteal formation of new bone. All the bones of the forearms and lower legs show changes practically throughout the shafts, the layer of new bone varying from one-sixteenth to one-quarter of an inch in thickness and being most pronounced at the distal ends. The outline is fairly even. The lower femur is slightly changed. No other bones of the skeleton are found changed.

The only joints showing any changes are the knees. Here the periarticular soft parts are evidently thickened. There is considerable proliferation of the epiphyseal portion of the bones forming the joint, the irregular new bone extending to the cartilage border and in a few places there is actual lipping, as in osteo-arthritis. The interarticular cartilages are a trifle more irregular than normal.

The patient was admitted to the wards Jan. 8, 1908, where she remained until Jan. 16, 1908. While in the hospital paracentesis of the chest was done and 16 ounces of clear, serous fluid withdrawn.

Soon after discharge the patient went to her home in Nova Scotia and nothing is known of her condition since.

## DISCUSSION

No summary of the recorded cases of secondary hypertrophic osteo-arthropathy has been made since 1906 when Alexander[3] published a synopsis of seventy-seven typical cases. As this author has apparently overlooked a few genuine cases of this disease, and as a considerable number have been published since the appearance of his paper, I have for purposes of discussion later, attempted an analysis of all the examples in medical literature with reference to the primary disease. As the description in many instances is extremely meager and no post mortem or Roentgen-ray examination is recorded, the selection of typical cases must be a somewhat arbitrary one. In the following col-

lection I have included only those in which the clinical picture was absolutely typical, or in which a post mortem or Roentgen-ray examination showed the presence of lesions in the bone characteristic of this disease.*

JANEWAY'S CASES

CASE 1.—Male, aged 35; nine months' history of cough with evidence of chronic empyema communicating with a bronchus eight months after onset of primary lesion, pains in ends of the long bones coincident with enlargement of hands. Extreme clubbing of finger-ends; cyanosis and definite bone enlargements of wrists and fingers.

CASE 2.—Male, aged 34; indefinite history; aortic endocarditis, irregular fever and chills accompanied by severe pains in ankles, knees and wrists. Swelling of extremities, followed three or four months later by extreme clubbing of the fingers (toes less); marked enlargement and some tenderness of the lower ends of the long bones. There was no fluid in the knee joints and the fingers were not cyanotic. Primary lesion probably a *Streptococcus viridans* endocarditis.

CASE 3.—Male, aged 29; history of appendicitis four years before; pain in the right chest for five months; dyspnea, loss of weight, enlargement of extremities for few weeks and pain in wrist and ankles. Signs of fluid at right base; enlarged liver; secondary anemia. Distinct clubbing of the fingers, without cyanosis, and enlargement of the bones, both wrist and ankle. Radiographs by Dr. Cole showed definite though not extensive bone changes of osteo-arthropathy. Five weeks after he was first seen he coughed up blood and chocolate-brown pus, characteristic of a liver abscess, and a month later the enlargement of the wrists and fingers diminished. Complete recovery, and four years later in perfect health, when Roentgen ray showed that the enlargement of the soft parts had greatly diminished and that there was no change in contour or structure of the bones of the hand or arm.

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* The following cases (Abadie,[1] Armour,[5] Bailly,[9] Béclère,[17] Bernhardt,[20] Chatin and Cade,[25] 2; Chauffard,[26] Combemale and Chatelin,[27] Combemale and Sonneville,[28] Emerson,[31] Fischer,[35] Flückiger,[36] Gibson,[40] Gilbert and Fournier,[42] Gilbert and Lereboullet,[43] Gillett,[44] Godlee,[45] 3; Gouldesbrough,[46] 5; Gries,[47] Groedel,[47] Hartung,[52] 2; Hillier, unpublished, Hirschfeld,[54] 3; Hoffmann,[56] Jamet,[57] Joffroy,[60] Jovane,[61] 3; León y Avilés,[164] 4; Macewen,[167] Maeshima,[169] 5; Marfan,[113] 3; Marie,[114] Marina,[116] 2; Miller,[120] Möbius,[124] Moizard,[125] 2; Moussous,[127] Murray,[130] O'Carrol,[132] Orillard,[134] Parmentier and Castaigne,[136] Pidcock, unpublished, Puyhaubert,[144] Reed,[149] Reynaud and Audibert,[153] 5; Rotch and Dunn,[155] Ruehle,[157] Saundby,[161] Schmidt,[163] Schou,[164] Sevestre,[165] Smirnoff,[173] Taylor,[183 184] Thompson,[182] Thorburn,[180] Variot and Chicotet,[189] Vas,[200] Vedel,[208] Villard,[214] West,[224] 2, although in many instances included by one or more of the previous writers as cases of hypertrophic osteo-arthropathy, I have excluded since the clinical report, while giving evidence of clubbing of the fingers and toes, makes no mention of the characteristic changes in the long bones. Many are probably true examples of this condition, but the description is so incomplete as to make them of no value. Twenty-two other cases which are mentioned in the literature of hypertrophic osteo-arthropathy (Chrysospathes,[38] Elliott,[39] Field,[44] Fraentzel,[48] Friedrich[62] and Erb,[53] 2; Gasne,[62] Gerhardt,[64] Gessler,[67] Guérin and Etienne,[73] Hirtz,[86] Jolly,[89] Koll,[94] Legrain,[100] Méry and Guillemot,[119] Postmantir,[140] Sollier,[170] Spieler,[172] Tournier,[195] Verstraeten,[205] v. Recklinghausen,[147] Virchow[207]), I have excluded as being examples of other conditions than the one under consideration. In only a few is there evidence even of true clubbing of the fingers. The papers by Fragle[58] and Mestre[139] I have not been able to obtain.

TABLE 1.—PUBLISHED CASES GROUPED ACCORDING TO THE PRIMARY DISEASE

A. DISEASES RESPIRATORY TRACT

| | | |
|---|---|---|
| Abscess of lung | 1 | Kerr.[90] |
| Bronchiectasis | 27 | Alexander,[3] 4; Bamberger,[13] 6; Botez,[24] Brooks,[29] 2; Dennig,[46] Doebblin,[46] 2; Emerson,[51] Freytag,[61] Godlee,[73] Janeway,[88] Maguire,[100] Massalongo,[117] Mosti,[120] Sitta,[167] Thompson,[192] Wynn,[218] 2. |
| with emphysema | 2 | Brooks,[29] Gillett.[71] |
| with empyema | 2 | Godlee,[73] Thayer.[192] |
| with infantilism and lymphatism | 1 | Franchini.[60] |
| with meningitis | 1 | Brooks.[29] |
| with pleurisy | 1 | Thayer.[192] |
| with pulmonary tuberculosis | 3 | Bamberger,[13] Emerson,[51] Janeway.[88] |
| with pulmonary tuberculosis and spinal caries | 1 | Walters.[211] |
| with chronic nephritis | 1 | Brooks.[29] |
| with syphilis | 1 | Van Deventer.[197] |
| Bronchitis | 5 | Blakeney,[22] Brooks,[29] Edgar,[49] Genova,[64] Stockman.[180] |
| with emphysema | 1 | Thiroloix and Jacob.[189] |
| with emphysema and syphilis | 1 | Reynaud and Audibert.[153] |
| with pleurisy | 2 | Emerson,[51] Pichard,[139] |
| with pneumonia | 2 | Stembo,[175] Roubinovitch.[156] |
| with pneumonia and cardiac dilatation | 1 | Brooks.[29] |
| with pulmonary tuberculosis | 1 | Salles and Halipré.[159] |
| Cyst of lung (hydatid) | 1 | Thoinot and Delambre.[190] |
| Empyema | 8 | Bondi,[26] Genova,[64] Janeway,[88] Lefebvre,[99] Rauzier,[149] Rendu and Boulloche,[151] Thayer,[192] 2. |
| with bronchiectasis | 1 | Démons and Binuad.[44] |
| with bronchitis | 2 | Davis,[42] Mouisset et Orsat.[128] |
| with chronic nephritis | 1 | Emerson.[51] |
| with adhesive pericarditis | 1 | Springthorpe.[174] |
| with pneumonia | 1 | Thompson.[191] |
| with pulmonary tuberculosis | 1 | Prokop a Stretti.[143] |
| Influenza | 1 | Redmond.[140] |
| Malignant disease— | | |
| Cancer lung | 1 | Thompson.[192] |
| Cancer mediastinum | 1 | Strangeways and Ponder.[181] |
| Cancer mediastinum, lungs and pleura; endocarditis | 1 | Ewald.[58] |
| Lymphadenoma of mediastinum | 1 | Weber.[212] |
| Sarcoma of lungs | 4 | Alexander,[3] Cagnetto,[33] Hall,[79] Saundby.[169] |
| Sarcoma of mediastinum | 1 | Hasbrouck.[69] |
| Pleuritis, effusion | 1 | Sternberg.[178] |
| Pneumonia | 1 | Barot and Pichard.[18] |
| with bronchitis | 1 | Brooks.[29] |
| with endocarditis, chronic nephritis | 1 | Schittenhelm.[162] |
| Streptothrix of lungs | 1 | Landis.[86] |
| Pulmonary tuberculosis | 16 | Brooks,[29] Curl,[40] Harris,[81] Landis,[86] Lockwood,[106] Maguire,[100] Massalongo and Gasperini,[118] Mestre,[120] Métin and Guillion,[123] Mettenheimer,[122] Spillmann and Haushalter,[173] Steven,[179] Teleky,[185] Thérèse,[187] Thompson,[191] Thorburn.[195] |

TABLE 1.—(Continued.)

| | | |
|---|---|---|
| Pulmonary tuberculosis— | | |
| with aortic insufficiency | 1 | Bamberger.[33] |
| with empyema | 2 | Gouraud[75] and Marie,[133] Packard.[187] |
| with pleurisy with effusion; aortic stenosis | 1 | Waldo.[200] |
| with spinal caries | 2 | Thorburn,[192 194] Whitman.[210] |
| with stenosis of esophagus | 1 | Hartung.[92] |
| | 108 | |

B. DISEASES CIRCULATORY TRACT

| | | |
|---|---|---|
| Aortic insufficiency | 1 | Bamberger.[33] |
| Congenital heart— | | |
| Defect of septum | 1 | Shaw and Cooper.[188] |
| Pulmonary stenosis | 1 | Bamberger.[33] |
| Endocarditis | 1 | Janeway.* |
| Mitral stenosis; hydatid cyst of liver | 1 | Thorburn.[193] |
| Pulmonary stenosis; aortic insufficiency | 1 | Bamberger.[33] |
| | 6 | |

C. DISEASES ALIMENTARY TRACT

| | | |
|---|---|---|
| Abscess of liver | 1 | Janeway.* |
| Abscess of liver, empyema and syphilis | 1 | Reed.[149] |
| Hypertrophic biliary cirrhosis | 6 | Gilbert et Fournier,[69] 2; Obermayer,[131] 3; Van den Bergh.[196] |
| Chronic enteritis | 2 | Renner,[152] Telkey.[165] |
| Chronic jaundice | 3 | Obermayer,[131] 2; Décloux and Lippmann.[43] |
| | 13 | |

D. MISCELLANEOUS

| | | |
|---|---|---|
| Abscess of axilla, syphilis, pulmonary tuberculosis | 1 | Newton and Mercelis.[159] |
| Abscess salivary gland | 1 | Wolfsohn.[217] |
| Cancer of breast, neck, larynx, thyroid | 1 | Kruger.[85] |
| Polyuria | 1 | Apert and Rouillard.[4] |
| Spinal caries; amyloid disease | 1 | Thompson.[192] |
| Syphilis (congenital), jaundice | 1 | Thompson.[200] |
| Syphilis; pelvic abscess; pulmonary tuberculosis with cavity | 1 | Chrétien,[25] |
| | 7 | |
| No known antecedent disease | 5 | Gluzinski,[72] Reed,[149] Soltau,[171] Symons,[182] van der Weijde en Buringh Boekhoudt.[196] |

* Through the courtesy of Dr. Janeway I am able to give a summary of three of his unpublished cases.

Hypertrophic osteo-arthropathy is so generally secondary to some obvious primary disease that the occasional recorded instances which are apparently without relation to some antecedent disease are worthy of careful consideration as particularly affecting the question of etiology. In all, twenty-one such examples are quoted in the literature. Case 1 of this report must also be discussed with this group.

Gerhardt's[66] case, although accepted by Wynn[218] and Janeway[88] as a true case of hypertrophic osteo-arthropathy, seems to me from the description given to be more characteristic of acromegaly, as an example of which it was published. The case of Gessler[67] likewise should be classified as probable acromegaly. Postmantir's[142] case is doubtful, although the fingers are mentioned as clubbed. Guérin and Etienne[78] conclude that their case is not a true example of Marie's type. Schmidt[163] published a very meager history of a woman of 48 with hypertrophy of the ends of the fingers and toes, but without mention of bone changes, in which the only antecedent diseases were rheumatism and acquired syphilis twenty-three years previously. Improvement with potassium iodid is recorded. The case does not appear typical and, indeed, one is left with the impression that the condition is probably entirely due to the luetic infection. These five cases then can be eliminated without further discussion as atypical or doubtful.

The remaining sixteen cases are all probably examples of osteo-arthropathy, although in several instances the history is somewhat meager. In three of them (Apert and Rouillard,[4] Gouraud[75]-Marie,[113] Lockwood[106]) a definite disease is mentioned which seems clearly to have been the primary condition, and these should consequently be excluded. In eight others the past history is so suggestive of a primary basis for the osteo-arthritic changes that they cannot be accepted as unquestioned examples of primary osteo-arthropathy. Brooks,[29] in commenting on his own case (No. 5), states that, while no pulmonary lesions can be demonstrated, the history of many previous attacks of bronchitis makes it quite probable that it is one of pulmonary origin. Wolfsohn's[217] patient, a man of 34, had an operation for inflammation of the salivary gland at 24, soon after which he first observed the changes in the fingers. The author expresses the opinion that the osteo-arthropathy may have been secondary to this inflammatory process. He acquired syphilis two years after the diagnosis of osteo-arthropathy was evident. In one (Décloux and Lippmann[43]) there is an indefinite previous history of icterus, erysipelas of both lower legs and synovitis. In the case of Newton and Mercelis,[120] a man of 33, there was a family history of tuberculosis with a personal history of a morning cough for years. He was rejected four times for the army because of "weak chest." Twelve years previously he had an ulcer on

the penis, presumably the primary lesion of lues. At the time of the observation he entered the hospital for a large axillary abscess, which, after operation, ran a very protracted course. Salles and Halipré's[150] case had a family history of tuberculosis and he had had, five years previous to the first observation, a severe and obstinate bronchitis. There were also indefinite signs in the lungs at the time the condition in the bones and joints was described. Spillmann and Haushalter[173] state that in their case the signs of the disease appeared a year previous to the development of pulmonary tuberculosis. In view of the fact that pulmonary tuberculosis is frequently of very insidious type and may exist for many years before being recognized, it would seem probable that an unrecognized tuberculosis of the lungs was the focus. Similarly in Steven's[170] case there is evidence of a more or less chronic process in the lungs with cough, but at the time of entrance to the hospital no signs of disease were found in the chest. Thiroloix and Jacob[169] publish their case as one of the primary type and the lungs as normal, but in the history state that he was a chronic sufferer from tracheobronchial catarrh and emphysema. While it is impossible in the above eight cases to state precisely the primary disease, the presence of some condition known to cause changes characteristic of osteoarthropathy is so strongly suggested by the history in each that it seems fair to challenge them as primary cases.

There remain then but five cases which offer any definite positive evidences of the existence of a primary type of hypertrophic osteoarthropathy (Gluzinski,[72] Reed[149] (Case 4), Soltau,[171] Symons,[182] Van der Weijde en Buringh Boekhoudt[198]). Each author particularly states that there was no antecedent disease and the histories are uniformly without definite suggestion of such, although in several the clinical description is meager. In Soltau's case the patient gave a history of a severe attack of influenza eighteen months previously, but no signs or symptoms of any pulmonary disease remained. These cases lose much of their significance, due to the fact that in none was a post mortem examination made, without which it is impossible to state positively that no primary disease was present. Mention is made of a Wassermann reaction in only two and a tuberculin test in only one. It is very reasonable, then, to consider that some cardiac or pulmonary condition, some obscure focus of infection or a liver cirrhosis, might have existed without being manifest.

Furthermore, it may be possible that in rare instances osteoarthropathic changes may, when once well established in the tissues, and contrary to the usual course of the disease, become progressive in spite of healing of the original infectious focus. Such may have taken place in Case 1, described in this paper. It is evident from the history

that in 1906 he suffered from a very severe infection, the nature of which is not evident from the patient's description nor from the post-mortem examination. The appearance of the symptoms in the joints and bones which were observed by the patient two years subsequently makes it seem probable that these were induced by this acute illness. The earlier disease, however, entirely disappeared, leaving no traces of its nature, while the osteo-arthropathy irregularly but gradually advanced. The malignant disease of the left lung found at necropsy may have existed longer than would be indicated by the history, but repeated roentgenograms failed to demonstrate any abnormal process in the lungs until 1913, while the patient observed the first signs of the osteo-arthropathy in 1908.

We are justified, I believe, in taking the grounds that the six cases just cited suggest the possibility only of a primary form of osteo-artropathy. If such a type does exist, it is indeed strange that among the large number of cases in the literature none is to be found which is indisputably primary. On the other hand, as Brooks states, one is struck with the constancy of evidence that hypertrophic osteo-arthropathy is the result of some primary disease.

The considerable number of post-mortem examinations on cases of this disease together with Roentgen-ray studies during recent years leaves no question as to the essential features of its pathology. So far as the skeleton itself is concerned, the changes consist primarily in a slowly progressive, ossifying periostitis beginning usually in the distal ends of the diaphyses of the bones of the forearm and lower legs, later involving also the other bones of the limbs and even in some cases nearly all the remaining bones of the skeleton. Later in the course of the disease and coincident with the periosteal proliferation, there is also a rarefying osteitis of the shafts with fatty changes in the marrow. Various authors of recent years seem to be in agreement as to the exact nature of the histological changes taking place, and these need not be discussed here. A study, however, of a series of cases over a long period of years by means of frequent Roentgen-ray examination has afforded the author an opportunity for close observation as to the extent of the affection of the bone in advanced stages of the disease and the changes which take place at various periods.

In the first place, it does not appear to be generally recognized that the changes in the skeleton in a well developed case of secondary hypertrophic osteo-arthropathy are seldom confined to the bones of the forearms, hands, lower legs and feet as so often described. In Case 1, for example, the alterations were almost general. In fact, it may be stated that a Roentgen-ray examination in these cases always reveals skeletal changes of greater extent and of a more marked type than is at first evident.

In his original paper, Bamberger[13] says that in the long existing cases the periostitis ossificans leads to thickening and condensation of the cortex and that here we have a later stage of the process which is seldom seen because in most instances the primary disease has led to death earlier. This transformation has been observed several times in the cases described above. While at first the new subperiosteal bone is sharply differentiated from the old shaft, at a later period, that is, usually after a lapse of two or three years, the two become more or less fused and in most places are indistinguishable. Judging from our own observations only, this transformation appears to occur in those cases which remain more or less stationary as well as in those which have a chronic progressive course. Accompanying this fusion just mentioned in the late stages of the disease, the entire structure of the bones, especially those most involved, becomes entirely altered. In the most extreme cases there remains scarcely any of the appearances of the original bone. Instead the osseous tissue appears very thin and of a coarse, irregular structure, in general very closely resembling the appearances seen in typical cases of osteitis deformans. I have never seen, however, any curving of the bone or deformity, except in outline, as is so characteristic in this latter disease. As a late manifestation, I have once or twice seen evidences in individual bone of a characteristic atrophy, although as a rule the process is primarily one of hypertrophy. These changes just described are admirably shown in Figures 5, 6, 7 and 8.

The statement made by most authors that the changes in the bones are confined essentially to the diaphysis is wide of the truth. While the process does probably invariably begin in the diaphysis as shown in Figure 10, yet all well-established cases show a very marked new formation of bone in the epiphyseal portion. It is usually much less regular than the sheath about the diaphysis and apparently much less rich in lime salt, appearing as a mossy, faint deposit in the roentgenogram, which most commonly stops abruptly at the line of the joint surface. This is well indicated in Figures 5, 6 and 8. These latter changes closely resemble, or are even identical with, the appearances seen in cases of acromegaly.

The Roentgen-ray examinations of the first four cases indicate very clearly that the process in the bones follows a course parallel to the slowly progressive clinical course. That the almost extraordinary diminution in the size of the affected parts which has so often been observed during the periods of remission, is due primarily to changes in the soft tissues rather than the bones, cannot be doubted, but in three of my cases (Cases 2, 3 and 4) there has been observed after varying periods an unmistakable retrogression in the bony growth which has led to a slight diminution in the size of the bones themselves.

There is an almost compiete unanimity of opinion among authors on this subject, that the clubbing of the fingers and toes in cases of secondary hypertrophic osteo-arthropathy is due entirely to changes in the soft parts. I have found but three writers who record changes found in these bones by the Roentgen ray. Gouldesbrough[74] states that in his cases there was definite proliferation in the distal phalanges. Teleky[165] says that increase in the size of these bones is rarely seen, and reports one case in which the Roentgen ray showed a slight deformity of two only. In a single case, Kruger[95] demonstrated mossy deposits in the diaphysis of the end phalanges. In my cases more or less marked changes were found in all five. In two they were slight, but in the remaining three very noteworthy (Figure 9). The changes noted in these five cases consisted essentially in a proliferation of the distal half of the last phalanges, usually giving the "burr form," but occasionally with immense burr-like processes as seen in Figure 9.

Considerable controversy has centered about the question of the pathological processes accompanying the constant and usually striking objective signs in the joints adjacent to the affected bones. Many of the older writers have claimed that the changes were entirely confined to the periarticular tissues, the interarticular cartilage always remaining intact and unchanged. The more recent writers are largely in accord in their description of the pathology of the joints, and nearly all admit that besides the thickening of the periarticular tissues and the presence of effusion, there are, at least in the most developed cases, changes in the cartilage as well. It is commonly more or less eroded and in rare instances has entirely disappeared. Reynaud and Audibert,[153] and Ball and Alamartine[11] describe true osteophytes as occasionally occurring and even a considerable degree of ankylosis as a result. All of these lesions have been present in my cases, and, clinically, the severe symptoms and disability have been due largely to the conditions in the joints. In Case 1, for example, for a long time at the beginning the symptoms were entirely confined to the joints, and throughout the course of the disease the symptoms were referred very largely to these parts.

Several authors have in individual cases described a marked irregularity in the course of the disease which my observations on four of the above cases followed for a considerable time seem to show to be characteristic. It is a common observation that cases of simple clubbing occurring secondary to such diseases as empyema, quickly return to normal size and appearance after the evacuation of the pus. Only a few cases of hypertrophic osteo-arthropathy, however, are on record in which similar changes have taken place, and only a few of these were observed by the Roentgen rays with reference to the possible

participation of the bones in this retrograde process. Thompson[191] lays particular emphasis on the fact that clubbing may entirely disappear with improvement in the primary disease, but states that there is no evidence that absorption of the newly-formed bone ever occurs. In Gillett's[71] case considerable improvement in the fingers and toes followed almost immediately the drainage of the empyema, but the condition in the bones was not studied by means of the Roentgen rays. Thorburn[193] likewise in one case of phthisis with cavity, after drainage, and a second of empyema, after operation, speaks of retrogression in the clubbing of the fingers. Godlee's[73] case of bronchiectasis and empyema developed clubbing after four months, which disappeared ten weeks after the cessation of expectoration. Schittenhelm[162] studied his case by means of skiagrams and found that the diminution in the swelling was confined entirely to the soft parts, the affected bones remaining unchanged. Alexander[3] notes an improvement following the improvement in the primary bronchiectasis. At the time the case was published the lung condition was practically normal and the joint symptoms and swelling had entirely disappeared. The bones did not seem enlarged and skiagrams showed that the new bone had become more dense and so closely fused with the old shaft that the line of division was only to be made out in places. These changes in the bones are evident in Plates III and IV of his article. The author speaks of this as a unique case. Relief of symptoms in the joints and the pain in Botez's[24] case of bronchiectasis and gangrene of the lungs followed the treatment of the lung condition. Likewise in Barot and Pichard's[15] case, the improvement in the pneumonia following treatment resulted in an improvement in the general condition and especially the joint symptoms.

In Case 5 of my series, no opportunity was offered to study the course of the disease as the patient was under observation only a few days; but in the other four which were studied for a period of years there was a very extraordinary variation in their course. In Cases 2, 3 and 4 the alternating periods of exacerbation and retrogression constantly followed an increase or diminution in the activity of the primary disease. The course in Case 1 is most interesting. Exactly the same variations were noted throughout the period of nearly six years while under observation, although no primary disease was ever found. At times the symptoms in the joints were very acute and accompanied by enormous swelling and stiffness, with evident increase in the degree of clubbing of the fingers and toes. Following these periods there were intervals of weeks or months when the symptoms of pain almost entirely disappeared and the swelling and clubbing diminished materially. The bones were studied at frequent intervals

during the entire period of observation by means of the Roentgen rays and never gave any evidence whatsoever of any retrogression in the bony changes, though for considerable periods coincident with the remissions in the clinical course, the process appeared to be at a standstill. As stated in the history of the case, the explanation of this is probably found in the fact that the disease ran a chronic and irregularly progressive course. As in Alexander's[3] case, the new bone in many cases became closely fused with the old, but never less in thickness. The course of the process in Case 2 is especially noteworthy. On March 24, 1913, the patient was readmitted to the hospital apparently in a dying condition. There was a generalized tuberculosis involving both lungs, with signs of a large cavity on the left and a very abundant putrid expectoration. There was also cardiac decompensation and a tuberculous enteritis. Signs of the osteo-arthropathy were very striking and much more marked than previously. After a year's residence in the hospital, the patient showed the extraordinary improvement in general condition which sometimes occurs in advanced pulmonary tuberculosis. The enteritis had entirely disappeared, the heart had become perfectly compensated, and the condition in the lung essentially quiescent. The sputum, likewise, had practically entirely disappeared. All the symptoms and signs in the arms and legs showed a corresponding and surprising improvement. There was still slight enlargement of the lower forearms and lower legs, with slight swelling of the wrists, ankles and knees and a moderate clubbing in the fingers and toes. The changes previously noted in the bones of the hand and especially in the terminal phalanges had literally almost disappeared. The layer of periosteal new bone in the forearms and legs was much thinner, more dense and, except in a very few places, formed a part of the original shaft. In this case, then, there was an unmistakable process of resorption. Exactly the same type of retrogression in the newly formed osseous tissue was observed in Case 3. Case 4 has been under observation for eleven years. During the first year of this period the patient was operated on for the empyema, which promptly healed and he has had no return of symptoms. For the past nine or ten years the bronchiectasis has been quiescent and the patient at work constantly, seemingly in good general health. The condition of osteo-arthropathy has apparently remained absolutely unchanged. There are no symptoms in the joints or long bones. During the first few years there was unmistakable evidence in the roentgenograms of a process of retrogression in the bone, but during recent years they have remained unchanged.

From these observations it seems fair to conclude that there is in hypertrophic osteo-arthropathy a characteristic irregular clinical course

with exacerbations and remissions following increased activity or improvement in the primary disease. These fluctuations in local signs are largely due to changes in the soft parts, although it is probable that in many instances a similar variation, but of less marked degree, takes place in the osseous tissue as well. It is possible that in some of the early cases perhaps of the acute type, the bones, if not too much affected, may, with the cure of the primary disease, return to their normal size. It is probable, as Lemercier[103] suggests, that when the osteo-arthropathy has passed the first stage, the retrogression is never complete. There can be little doubt that in a large number of cases, following the cure of the antecedent disease, the osteo-arthropathy becomes in a strict sense quiescent. Case 1 of my series suggests that rarely the disease, once well established, may continue progressive quite independently of the original disease focus.

The rôle played by pulmonary tuberculosis as a cause of hypertrophic osteo-arthropathy has been frequently discussed and several authors have commented on the relative infrequency with which osteo-arthropathy occurs in association with this disease. Alexander[3] collected seventy-seven typical cases of hypertrophic osteo-arthropathy from the literature and among them found fifteen of pulmonary tuberculosis, or 19 per cent. Janeway[88] collected ninety-three typical cases, sixteen associated with pulmonary tuberculosis, or 17 per cent. Wynn[215] found one hundred cases with eighteen, or 18 per cent. of tuberculosis of the lungs. The literature to date contains 139 cases which, with the five here recorded, make a total of 144, of which thirty followed pulmonary tuberculosis, or 20 per cent. Three of the five patients here reported were suffering from this disease. These more recent figures distinctly emphasize the importance of pulmonary tuberculosis in the etiology of osteo-arthropathy. The explanation of the fact that pulmonary tuberculosis, which is such a common disease of the lung, in comparison with bronchiectasis, which is more frequently the cause of osteo-arthropathy, is perhaps found, as Thompson suggests, in the fact that in pulmonary tuberculosis there is usually but a slight degree of toxemia, and the fact that the secretions from the lungs are easily raised and therefore not so effective as in the case of bronchiectasis as foci of infection. Figures from Groups B, C and D reported in this paper still further emphasize the importance of pulmonary tuberculosis as the etiological factor in the disease under discussion. In all, among the thirty-nine miscellaneous cases studied, nineteen were pulmonary tuberculosis, and of these six showed changes in the long bones typical of osteo-arthropathy, or 50 per cent. of Group C which showed the lesions of osteo-arthropathy. If simple clubbing of the fingers is to be considered as merely an early stage of

osteo-arthropathy, as I believe can be shown from a study of these groups, then tuberculosis of the lungs will take first place in the list of diseases inducing these bone and joint changes.

### THE RELATIONSHIP OF SIMPLE CLUBBING TO SECONDARY HYPERTROPHIC OSTEO-ARTHROPATHY

Although much has been written concerning the possible relationship of these two conditions, writers on the subject are far from an agreement, and it must still be regarded as an open question. The confusion in the literature is evident from the fact that although most authors restrict the term secondary hypertrophic osteo-arthropathy to those cases showing alterations in the long bones as well as clubbing of the fingers, a considerable number of cases of simple clubbing of the fingers have been reported as examples of this disease. By far the majority of authors consider these two conditions at least closely related if not identical. Bamburger[13] published three cases in which there were no changes except the hippocratic fingers, but which at post mortem examination were found to have periostitis of the long bones, and concludes from his observations that the clubbing in the distal phalanges is simply the first stage of osteo-arthropathy and that both conditions are co-effects of the primary disease. Marie[113] believes that the hippocratic fingers seen with various lung diseases are not essentially different from those observed with osteo-arthropathy. Lefebvre[99] argues that both are phenomena of the same order. Thompson[192] maintains that a common cause exists for both and that the drumstick fingers are simply the initial stage of osteo-arthropathy. Landis[98] argues that since both are associated with the same primary conditions, that osteo-arthropathy is always accompanied by clubbing of the fingers and toes, and that some cases of simple clubbing have shown changes in the long bones, this should be regarded as an incipient or arrested stage. Wynn,[218] in the conclusion of a long discussion, says "One is forced, I think, to the conclusion that simple, ordinary clubbing is but the early stage of the condition which in later stages is termed osteo-arthropathy. It is produced by a lesser action of the same causes, which are probably toxic." Janeway[88] is of the opinion that they are different stages of the same process. Lemercier[103] regards club fingers as an abated form of osteo-arthropathy or the latter in process of evolution. Essentially the same view of the close relationship between these two conditions is held by various other authors including Rauzier,[146] Walters,[210] Géraud,[65] Reynaud and Audibert,[153] Möbius,[124] Vedel,[203] Villard,[206] Comby,[39] Teleky[185] and others. Rendu and Boulloche,[151] on the other hand, are emphatic that hypertrophic osteo-arthropathy should not be confounded with digital deformities

occurring with other diseases, especially those producing cyanosis. Genova[64] contends that an essential difference exists between the two. Labrit[97] believes them to be independent conditions. Béclère[17] and Dennig[45] found no osseous lesions in their cases of hippocratic fingers and therefore maintain that this condition is distinct from hypertrophic osteo-arthropathy. Bezancon and Jong[20] made an exhaustive study of the subject and differentiate the two conditions as follows: First, in hippocratic fingers the process is always limited to the end phalanges, irrespective of the length of the causal diseases, while in osteo-arthropathy there are always multiple deformities of the bones and joints; second, pain and functional immobility, which are always present in the latter condition, are never seen in the former; third, pathological changes in simple clubbing consist entirely in hypertrophy of the soft parts, while in osteo-arthropathy lesions are osseous, articular and periosteal; fourth, no case of osteo-arthropathy is recorded which began as simple clubbing. They conclude that the two conditions have no relation to each other.

In an effort to settle this question, I have, during the past few years, studied a miscellaneous group of thirty-nine cases of simple clubbed fingers occurring with a considerable variety of diseases. A summary of these cases together with the results of Roentgen-ray examination and grouped according to the osseous lesions found, are given below.

### *Group B.—Twenty-Two Cases of Simple Clubbing with Changes Confined to Soft Parts**

Case 6.—F. A., male aged 20, Boston Consumptives' Hospital, March 26, 1914.

Chronic pulmonary tuberculosis, Stage III, with large cavity in left upper lobe. Symptoms marked, with dyspnea and cyanosis.

Marked clubbing in fingers and toes.

Case 7.—H. B., boy, aged 18. Patient under observation for the past ten years. Chronic abscess of left lower lobe, with typical signs, but very few constitutional symptoms. Patient in good general condition, at regular occupation and no symptoms except slight cough with occasional raising of moderate amount of rather foul sputum.

Fingers and toes moderately clubbed.

Case 8.—B. C., man, aged 39, Boston Consumptives' Hospital, Oct. 31, 1909.

Empyema with operation ten years ago; sinus still discharging. Old Pott's disease. Chronic pulmonary tuberculosis, Stage III. Patient, although not confined to bed, is very weak and emaciated. There is moderate dyspnea with exertion, but no cyanosis. Never noted any changes in the ends of the fingers, but for past two years has had nearly constant dull pains in the lower legs and the bones have been sensitive.

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* Systematic Roentgen-ray examination in each case failed to show any abnormalities in the distal phalanges, long bones or joints.

The ends of the toes and fingers are all strikingly clubbed, but without marked cyanosis or injection of the nail bed. The forearms appear normal but the lower legs are possibly a little enlarged, although the bones feel normal.

CASE 9.—W. C., woman of 50, Long Island Hospital, seen March 16, 1910.

The patient in last stages of pulmonary tuberculosis and confined to bed. Extensive process in lungs, with cavity formation.

Only slight clubbing of fingers and toes.

CASE 10.—A. D., a bartender aged 41, seen at the Boston City Hospital August 5, 1910.

Chronic alcoholism; cirrhosis of the liver with ascites; chronic pulmonary tuberculosis, Stage III. The patient is emaciated and very weak; considerable dyspnea.

All the fingers show moderate clubbing, which is most marked in the thumb and the next two fingers. Feet are similarly affected.

CASE 11.—J. E., man aged 32, seen at Long Island Hospital March 21, 1910.

Chronic pulmonary tuberculosis without cavity formation. Slight clubbing of fingers and toes.

CASE 12.—G. G., man aged 50, seen at Boston Consumptives' Hospital March 1, 1914.

Chronic pulmonary tuberculosis, Stage III, with cavity formation; marked toxemia. Considerable dyspnea and cyanosis. Recent severe hemorrhage.

Moderate clubbing of fingers and toes.

CASE 13.—E. K., man aged 40, seen at the Long Island Hospital March 19, 1910.

Pulmonary tuberculosis, Stage III; mitral stenosis and regurgitation; chronic alcoholism.

The fingers and toes show only a slight degree of clubbing.

CASE 14.—T. F. K., man of 30, entered the Boston City Hospital December 15, 1913.

Malignant endocarditis, with positive blood cultures on April 24, 1914. Death a few days later. No necropsy.

Clubbing of fingers and toes developed while under observation in the hospital and became fairly well marked.

CASE 15.—A. L., man aged 32, seen at the Long Island Hospital April 16, 1914.

Typical case of advanced pulmonary tuberculosis with extensive cavity formation; ambulatory, but in an extremely weak condition, with considerable dyspnea and some cyanosis.

All the fingers and toes are strikingly clubbed and the hands and feet appear clumsy and thickened.

CASE 16.—J. J. M., man aged 42, admitted to the Boston City Hospital April 10, 1910.

Pulmonary tuberculosis, stage III, with severe symptoms; chronic alcoholism.

Clubbing of the fingers and toes of moderate degree.

CASE 17.—T. P. M., man aged 33, seen at Boston Consumptives' Hospital April 24, 1914.

Pulmonary tuberculosis, stage III, without signs of cavity formation. Considerable cyanosis and dyspnea.

Moderate clubbing of fingers and toes.

CASE 18.—A. R., male aged 70, seen at Long Island Hospital March 21, 1910.

Arteriosclerosis; apoplexy; senile dementia; emphysema with marked dyspnea and cyanosis; no temperature. Patient died May 1, 1910.

Very moderate clubbing in fingers and toes.

CASE 19.—J. S., man aged 44, seen at the Long Island Hospital March 21, 1910.

Chronic alcoholism; chronic pulmonary tuberculosis with cavity formation; chronic interstitial nephritis; probable old syphilis. Patient died Oct. 21, 1910. No necropsy.

Moderate clubbing of fingers and toes.

CASE 20.—J. S., a woman aged 31, entered the Boston City Hospital April 13, 1913.

Chronic jaundice due to probable malignant disease of the liver; extreme emaciation with marked dyspnea. Lungs and heart normal. Patient died May 6, 1913. No necropsy.

Moderate clubbing of fingers and toes.

CASE 21.—P. S., man aged 21, seen at the Boston City Hospital May 6, 1913.

Aortic regurgitation and stenosis; chronic nephritis. Severe hemorrhage from gums and mucous membrane, with resulting extreme anemia. Unusually severe dyspnea with the slightest exertion.

Moderate clubbing of all the fingers and toes.

CASE 22.—A. S., male aged 59, seen at Boston Consumptives' Hospital March 5, 1914.

Chronic pulmonary tuberculosis, stage III, with extensive but inactive process. Occasionally some cyanoisis of fingers.

Moderate clubbing of fingers and toes.

CASE 23.—J. C. S., male of 68, seen at Long Island Hospital March 20, 1910.

Asthma since 12; mitral regurgitation with hypertrophy and dilatation of the heart; eczema; chronic interstitial nephritis; arteriosclerosis.

Moderate clubbing of fingers and toes.

CASE 24.—C. T., woman aged 22, entered Boston City Hospital April 1, 1910.

Infection with colon bacillus; septicopyemia and pyonephrosis.

Slight clubbing of fingers and toes developed while patient was under observation in the hospital. Nails deeply cyanosed.

CASE 25.—A. N. V., a boy aged 16, entered Boston City Hospital Dec. 23, 1913.

Pneumonia with complicating endocarditis and pericarditis. High, irregular temperature with marked dyspnea and anemia. Some cyanosis of the extremities.

Moderate clubbing of the fingers and toes, where the changes seem to be largely in the soft parts.

CASE 26.—T. W., a boy aged 4, entered the Boston City Hospital May 9, 1914, service of Dr. Lothrop.

Abscess of left lung since one year old, with very severe, persistent, spasmodic cough accompanied by a large amount of mucopurulent, occasionally bloody and moderately foul sputum. Fever and night sweats. Extensive and marked signs of cavity in the left chest.

The fingers and toes show a striking and typical condition of clubbing.

CASE 27.—R. W., a boy aged 11, entered Boston City Hospital Nov. 16, 1906.

Bronchiectasis with typical cough and sputum following pneumonia four years previously.

Jan. 26, 1910. The fingers and toes show a moderate degree of clubbing, although considerably less than formerly.

### *Group C.—Five Cases of Simple Clubbing with Changes in the Distal Phalanges*

CASE 28.—M. B., woman aged 40, Long Island Hospital, Feb. 13, 1909.

Chronic pulmonary tuberculosis, stage III, without signs of cavity. Patient died Jan. 23, 1912. No necropsy.

No alterations in the limbs except a slight degree of clubbing in the fingers and toes.

Roentgen-ray examination March 16, 1910. The distal phalanges of the hands show a slight proliferation in their outer half. The remaining bones of the skeleton and the joints were not examined.

CASE 29.—A. K., woman aged 61, seen at the Long Island Hospital March 16, 1910.

Chronic pulmonary tuberculosis without signs of cavity.

Characteristic clubbing of the fingers and toes of moderate degree.

Roentgen-ray examination March 16, 1910. Hands and forearms only. Considerable proliferation of the distal phalanges. Otherwise the bones and joints are normal.

CASE 30.—B. K., female aged 65, entered Long Island Hospital July 28, 1910.

Chronic bronchitis; chronic nephritis; arteriosclerosis with aortic roughening and mitral insufficiency. In August, 1910, an attack of pneumonia with delayed resolution. Died April 27, 1911. No necropsy.

Moderate clubbing of the fingers and toes.

Roentgen-ray examination Oct. 10, 1910, of hands and forearms only. The only abnormality made out is a moderate proliferation in the distal half of the last row of phalanges of the hands.

CASE 31.—N. McG., man aged 54, seen at Long Island Hospital March 19, 1910.

Pulmonary tuberculosis, stage III; arteriosclerosis with mitral insufficiency.

Moderate clubbing of the fingers and toes.

Roentgen-ray examination March 19, 1910, of hands and forearms only. The outer end of the distal phalanges are moderately ragged and show a marked proliferation. Arteries in the forearm show high degree of calcification. Joints normal.

CASE 32.—H. N., man aged 29, entered the Massachusetts General Hospital, service of Dr. R. C. Cabot, May 7, 1914.

Acute symptoms of nephritis with signs of old mitral stenosis and regurgitation, with decompensation and purpura. Marked edema of legs. No cyanosis.

The fingers and toes show a condition of marked clubbing, the type in the former being quite unique. The enlargement involves the entire last phalanx of the fingers, the swelling extending well down over the distal joint. In contrast to the usual rounded ends of the fingers they are almost square as though chopped off. The nails are unusually broad, a little thickened, and ribbed longitudinally, but are exceedingly short, in some instances being less than one-half inch. They do not present the usual parrot-beaked type.

Roentgen-ray examination May 12, 1914. The outer half of all the distal phalanges of the hand show a slight but definite proliferation of bone, the fan-shaped ends appearing more ragged and expanded than normal. On several of these phalanges of each hand at the joint end are small osteophytes resembling those seen in early osteo-arthritis. The joints, however, show no abnormal appearances. The bones of the forearms are likewise normal.

### *Group D.—Twelve Cases of Simple Clubbing with Changes in the Long Bones*

CASE 33.—R. B., male aged 38, Boston Consumptives' Hospital, March 27, 1914.

Advanced pulmonary tuberculosis; fibrosis without cavities. Very weak and emaciated; marked dyspnea and considerable cyanosis.

All the fingers and toes show moderate clubbing.

Roentgen-ray examination March 27, 1914. There are no clearly marked changes in the distal phalanges of the hand, but the other two rows are slightly thickened to a varying degree and in places show small but definite osteophytes. The right radius and ulna show a thin, subperiosteal deposit along the inner side of each for approximately the lower third. Similar changes are seen in the ulna and radius of the left forearm, but of lesser degree.

CASE 34.—A. E., a 32-year-old man, seen at the Boston Consumptives' Hospital, April 16, 1914.

Very advanced pulmonary tuberculosis without signs of cavity formation; febrile.

Very moderate clubbing of fingers and toes.

Roentgen-ray examination April 16, 1914. Bones of the arms and hands normal. The end phalanges of both feet are very irregular and show osteophytic outgrowths which are distinctly more than normal. In both feet the second, third and fourth of the first row of phalangeal bones show slight, somewhat irregular cortical deposits along the shaft. On the right similar changes are shown on the outer side of the first. The bones of the lower legs are normal.

CASE 35.—M. G., male aged 45, seen at the Boston Consumptives' Hospital April 14, 1914.

Very advanced pulmonary tuberculosis with extensive cavity formation; dyspnea and cyanosis striking.

Moderate clubbing of fingers and toes.

Roentgen-ray examination April 24, 1914. Beyond a very slight roughening in a few places along the first row of phalanges, nothing abnormal is noted in the bones of the hands. Feet normal except for marked enlargement and irregularity in the distal half of the last phalanx of one great toe. Along the outer side of the left tibia in its lower half there is a thin layer of cortical new bone and a similar layer along the inner side of the fibula for an extent of about 2 inches below the head. This latter deposit is ragged in outline and evidently contains almost no lime salts. The other bones of the limbs are not abnormal. Joints normal.

CASE 36.—G. C. P., a man aged 32, seen at Boston Consumptives' Hospital April 16, 1914.

Advanced pulmonary tuberculosis with cavity formation; extreme dyspnea with considerable cyanosis.

Marked clubbing of fingers and toes.

Roentgen-ray examination April 16, 1914. The distal phalanges are all strikingly changed. the normal fan shape being greatly exaggerated, the outlines extremely irregular. No other bones of the hands are altered. The distal phalanges of the feet seem a little more broad and irregular than normal. Both tibiae show a thin, irregular deposit of new bone varying from one-sixteenth to one-eighth of an inch in thickness along the inner side of nearly the entire upper half. The bones of the forearms show no abnormalities. Joints likewise normal.

CASE 37.—S. S., man aged 36, seen at Boston Consumptives' Hospital April 7, 1914.

Last stages of pulmonary tuberculosis with extensive cavity formation.

Marked clubbing in fingers and toes.

Roentgen-ray examination April 24, 1914. Bones of the hands and feet and forearms are normal. The right tibia along its outer surface from the epiphyseal line above nearly throughout half its extent shows a new layer of bone beneath the periosteum which in its thickest portion is about one-eighth of an inch. The left tibia shows a similar condition, but less well marked, for about one-third of its length only. The left tibia also in one place for a distance of about one inch shows a thin, irregular new layer. Fibulae normal.

CASE 38.—T. B. G., man aged 33, seen at the Boston City Hospital Dec. 27, 1910.

Severe bronchial asthma since ten; chronic bronchitis; chronic alcoholism; myocarditis. Considerable cyanosis of the extremities and marked edema of the lower legs.

A slight degree of clubbing in fingers and toes.

Roentgen-ray examination March 21, 1911. All of the end phalanges of the feet show a very unusual broadening out and are irregular in outline; the end

phalanges of the fingers somewhat less changed. Nearly all of the first row of phalanges of the hands show an irregular thin deposit of bone just beneath the periosteum. The long bones of the forearms and lower legs are negative. Joints normal.

CASE 39.—J. P. J., man of 28, seen at the Boston Consumptives' Hospital April 24, 1914.

Typical history of bronchiectasis since the age of 10, with signs of large cavity in the right lung; several attacks of pneumonia since, the last two years ago. Pulmonary tuberculosis which has apparently developed in the past few years. Lost left leg when 8 years old.

Never any symptoms in legs or arms or in joints until the past few months, when he has had slight swelling of the ankles, knees and wrists, with moderate dull pain and slight sensitiveness to pressure in these regions, especially over the bones.

Very striking clubbing of all the fingers and toes. The ankles, knees and wrists are slightly swollen, but no definite enlargement made out in lower legs and forearms.

Roentgen-ray examination April 24, 1914. Terminal phalanges of the hand very ragged, with definite proliferation of bone. Second row of phalanges in the fourth and fifth show very slight subperiosteal deposit of bone, more marked on the outer side. The first row shows slight but evident changes of this nature throughout, most marked on outer side. All the metacarpal bones show still more marked changes of this type, most evident in the thumbs. The ulnae and radii show definite characteristic deposits of bone beneath the periosteum, in one place on the right ulna approximately a quarter of an inch in thickness, the changes being mainly confined to the distal half, although in the right ulna throughout. In the lower portion of the diaphyses of the humeri a thin new layer easily made out. The carpals normal and no changes found in the joints of the arms and wrists.

The terminal phalanges of right foot not well shown, except the great toe, in which there is marked proliferation of bone. Second row of phalanges are normal, except for the great toe, which shows a thin layer throughout the shaft. Only the fourth and fifth of the first row show characteristic changes. Tarsus normal. The right tibia seems considerably enlarged, appearing massive throughout, but in many places no distinction is evident between the old cortex and the new layer of bone. Externally, however, the new shaft of bone can be easily traced through the two-thirds of the diaphysis from proximal end down; at about the middle of the tibia the new layer is a quarter of an inch in thickness. Down over the internal condyle there is a considerable formation of irregular new bone. At the head of the tibia there is considerable proliferation of bone of the same type from the epiphysis to the joint surface. Right fibula externally has a marked deposit of bone almost throughout its entire length, showing best in the middle third, where there is an irregular deposit varying from one-sixteenth to one-eighth inch in thickness. The ankle and knee joints present no abnormalities.

CASE 40.—J. B., man aged 41, Boston City Hospital, May 20, 1910.

Aortic and mitral disease with decompensation, anasarca; moderate cyanosis of the extremities; extreme dyspnea.

Since January, 1910, both knees and ankles have been considerably swollen and moderately painful, but without redness or tenderness. Patient died June 7, 1910. No necropsy.

The fingers and toes show marked clubbing.

Roentgen-ray examination May 2, 1910. The phalanges show no definite changes, but in all the metacarpal bones of the hand there is a thin subperiosteal layer of new bone. The ulna and radius of both forearms show the characteristic cortical new bone as a thin, somewhat irregular layer in the dis-

tal portion of the diaphyses. None of the bones of the feet is abnormal except that the fifth metatarsal in each shows a thin cortical layer throughout the entire shaft. The fourth metatarsal likewise shows a thin layer on its outer side. Approximately the lower third of the tibiae and fibulae show alterations like those described in the ulnae and radii. No changes in the joints are to be made out.

CASE 41.—J. L., man of 52, entered Boston City Hospital Jan. 14, 1910.

Chronic alcoholic; gonorrhea and chancroids many times but no history of lues; aortic regurgitation. Patient died Jan. 12, 1911, of cerebral hemorrhage.

All the fingers are markedly clubbed, especially on the right hand, and the feet show moderate changes of this nature.

Roentgen-ray examination Jan. 13, 1910. The end phalanges of the feet seem slightly more fan-shaped and ragged than normal, but the changes are not definite. Along the inner side of the left ulna in its upper third there is a definite thin, even layer of new cortical bone. Similar changes, but of much more marked degree, are seen in the right ulna and extending from the upper end to the junction of the middle and lower third. On its outer side and near the lower end there are a few thin, irregular deposits. Otherwise the bones of the skeleton are normal and the joints show no changes.

CASE 42.—J. M., bartender aged 41, Boston City Hospital, April 21, 1914.

Chronic alcoholism; cirrhosis of the liver; extreme dyspnea and ascites with considerable edema of the lower legs. No cyanosis, although nails are deeply injected.

Moderate clubbing of fingers and toes, most marked in thumbs and great toes.

Roentgen-ray examination April 21, 1914. Hands, feet, forearms and joints show no changes. Right fibula in upper portion both along inner and outer surface for a distance of 2 or 3 inches shows an irregular thin deposit, stopping sharply at the epiphysis. Similar changes are found in the left fibula. The outer border of the tibiae in several places is distinctly roughened, but no new layer of bone can be made out.

CASE 43.—H. C. S., woman aged 35, seen at the Massachusetts General Hospital, March 15, 1914, service of Dr. C. L. Scudder.

Paroxysmal cough for one year with large amount of greenish-brown, at times very foul, sputum. It is sometimes brought up in large amounts with change of position. Dyspnea with exertion.

Operation March 27, 1914; a large amount of foul pus evacuated from the left pleural cavity.

The fingers show a rather marked condition of clubbing; the toes also, but somewhat less.

Roentgen-ray examination March 16, 1914. Feet and legs not examined. Along the outer side of the metacarpal bone of the right thumb there is a definite thin subperiosteal layer of new bone. Similar changes in the lower left radius and ulna.

CASE 44.—J. E. T., an electrician aged 50, seen at the Massachusetts General Hospital April 15, 1914, service of Dr. C. L. Scudder.

Chronic tuberculosis of shoulder joint with pulmonary tuberculosis of twenty years' standing. Process evidently of fibroid type. No fever, cyanosis or dyspnea.

The fingers and toes show a moderate condition of clubbing.

Roentgen-ray examination April 17, 1914. The bones of the hands are normal except for a slight proliferation in many of the distal phalanges. The cortex of the tibia in several places is definitely thickened and slightly irregular in outline, but the line of separation between the old cortex and the new subperiosteal bone is not always to be made out. The bones of the forearm and the joints are normal. Roentgenograms of the feet not made.

The clubbing in the fingers and toes is said to be much less marked than in previous years. If this observation be correct, it is undoubtedly explained by the fact that the process in the lung is apparently quiescent, and that some time ago the infectious focus in the shoulder was obliterated through a section of the upper end of the humerus.

A summary of the results in these groups is given in Table 2.

TABLE 2.—Results of Roentgen-Ray Examination in Thirty-Nine Cases of Simple Clubbing of Fingers and Toes

| Disease | Bones Normal | Changes in Distal Phalanges Only | Changes in Long Bones | Totals |
|---|---|---|---|---|
| Pulmonary tuberculosis... | 10 | 3 | 6 | 19 |
| Bronchiectasis ..... | 3 | .. | 2 | 5 |
| Bronchial asthma, bronchitis ..... | .. | .. | 1 | 1 |
| Bronchial asthma, mitral disease ..... | 1 | .. | .. | 1 |
| Emphysema ..... | 1 | .. | .. | 1 |
| Chronic bronchitis, mitral disease ..... | .. | .. | .. | 1 |
| Cardiac disease ..... | 2 | 1 | 2 | 5 |
| Cardiac disease, pulmonary tuberculosis ..... | 1 | 1 | .. | 1 |
| Cirrhosis liver ..... | .. | .. | 1 | 1 |
| Cirrhosis liver, pulmonary tuberculosis ..... | 1 | .. | .. | 1 |
| Chronic jaundice (malignant disease liver ?).... | 1 | .. | .. | 1 |
| Septicemia ..... | 2 | .. | .. | 2 |
| | 22 | 5 | 12 | 39 |

An examination of Table 2 shows that twenty-two of the total thirty-nine cases, or 56.4 per cent., showed no changes in the distal phalanges or long bones, while five, or 12.8 per cent., showed alterations of varying degree in the ungual phalanges, and twelve, or 30.8 per cent., had periosteal proliferation in the long bones. Of this last group, six only showed ungual proliferation. A careful examination of these individual cases affords no explanation for these results; neither does the study of the primary condition yield anything significant. Furthermore, the degree of clubbing does not seem to correspond, except in a very general way, to the radiographic findings. The cases of Group D do on the whole present a more marked degree of clubbing than the other two. Bamberger,[13] Landis,[98] Reynaud and Audibert[153] and Teleky[165] mention cases showing proliferation in the end phalanges, but the changes in clubbed fingers are usually described as being confined entirely to the soft parts. The fact that eleven of

the above series of thirty-nine cases, or 28 per cent., have changes in these bones, would seem to prove definitely that the osseous tissue does participate in the changes to a far greater degree than is ordinarily supposed. The type of alteration is a definite and constant one, being usually confined to the distal half of the phalanx and consisting in an irregular hypertrophy of the bone, which in the most marked cases has a burr-like appearance, or, as one author has described, "a picture not unlike that of an electro magnet which has been dipped in fine iron filings." These appearances, both in type and distribution, seem to me exactly similar to those which have been observed in the end phalanges of the five cases of true hypertrophic osteo-arthropathy described in Group A, but are, on the whole, less marked.

It is exceedingly important to note that with the possible exception of Case 39, none of the cases in groups B, C and D gave any symptoms or showed any signs of changes in the joints or long bones, and yet twelve of these were shown by radiographic examination to have periosteal new bone formation. This bone proliferation seen in these twelve cases is of exactly the same type and general distribution as in the five cases in Group A. As in these cases of Group A, and of osteo-arthropathy in general, this hypertrophy was confined to the long bones in the forearms and lower legs, usually in their distal portions, and in a few instances the long bones of the hands and feet. From the history in Case 39 it seems certain that the clubbing of the fingers had existed for many years, while the slight symptoms in the joints were of but a few months' duration; in other words, this appears to be a case of hippocratic fingers which subsequently developed the lesions in the long bones characteristic of osteo-arthropathy. Since roentgenograms were not made previously, actual proof is lacking that this case began as one of simple clubbing and later evolved proliferation in the long bones; yet the previous history is so definite that such a sequence can hardly be doubted.

The question has very naturally been asked, if clubbed fingers is but an early stage of hypertrophic osteo-arthropathy, why has not the transition from the former to the latter been observed? A satisfactory answer is, I believe, found in the results of the examination of the thirty-nine cases recorded above. Although with the possible exception of Case 39, none showed any changes whatsoever in the joints or long bones of the limbs, systematic radiographic examination revealed the presence of typical early lesions of osteo-arthropathy in one or more of the long bones. Were the primary disease to be progressive, it can hardly be doubted, I believe, that these twelve cases would have shown more or less progressive lesions in the long bones and that at least some of the remaining twenty-seven cases would also later have developed

such lesions. The clinical experience of many observers indicates positively that while, as is well known, the clubbing in the fingers secondary to various conditions frequently appears quickly, the development of osteo-arthropathy seldom occurs earlier than at least three or four years after the appearance of the primary disease. The final test would consist in the Roentgen-ray examinations of a series of cases of early clubbing of the fingers occurring with such chronic progressive diseases as pulmonary tuberculosis and bronchiectasis, and subsequently for a period of years. So far as I am aware, no such studies have ever been made. Clinical evidence at least indicates that such is the sequence of events in a considerable number of cases of hypertrophic osteo-arthropathy in which the clubbing was noted for a long time previous to the appearance of symptoms and signs in the joints and long bones of the legs and arms.

Several authors have denied the identity of the type of clubbing in hippocratic fingers and osteo-arthropathy and have attempted to define the differences. It is undoubtedly true that the most marked types of clubbing occur in the well-developed cases of osteo-arthropathy. The finger-ends are more bulbous and the nails usually thicker, more striated and with a greater convexity. I have recently studied a large number of cases of hippocratic fingers occurring with phthisis and other conditions and have compared them with the clubbing in the five cases in Group A. I have been unable to satisfy myself of any differences except such as are to be explained on the basis of the difference in stage of development of the condition; in other words, in my experience the striking changes in the finger-ends in cases of hypertrophic osteo-arthropathy are strictly identical with those seen in hippocratic fingers, except that they represent a more accentuated form. In the rapidly developing type seen with empyema, for example, the swelling of the soft parts is extreme, the nail bed is deeply injected and swollen and the nails are red; whereas in the more chronic and slowly developing type seen with less virulent primary diseases, the swelling is less marked, the nail-bed is seldom injected and the nails are frequently cyanotic.

Every case of hypertrophic osteo-arthropathy so far recorded has shown well-developed clubbing of the fingers and toes, and it is regarded as an absolutely constant sign of the disease.

Finally, it is important to compare the primary diseases with which hippocratic fingers and hypertrophic osteo-arthropathy are associated. A comparison of the primary diseases in the thirty-nine cases of hippocratic fingers given in Table 2, with the primary diseases in a hundred and thirty-nine cases of osteo-arthropathy in the literature and given in Table 1, shows, in many respects, such a close correspondence

as to be very significant. As is perhaps to be expected, there is a considerably greater preponderance of pulmonary tuberculosis in Table 2. The correspondence between the pulmonary diseases taken as a whole in the two tables is very striking, however, being 72 per cent. of the total in Table 2 and 78 per cent. in Table 1. The individual diseases of the respiratory tract in Table 2 are naturally fewer in number because of the small total of cases, but are seen to be the diseases of the respiratory tract which predominate in Table 1. None is found in Table 2 which does not also occur in Table 1. The percentage of cases of osteo-arthropathy occurring with bronchiectasis is more than twice that of hippocratic fingers occurring with the same condition, whereas pulmonary tuberculosis and cardiac disease are far more common as the associated primary disease in the latter than in the former. It appears then as a result of this comparison that hypertrophic osteo-arthropathy and hippocratic fingers develop secondarily to the same general group of diseases.

Considering the facts then, first, that clubbing of the fingers always occurs in hypertrophic osteo-arthropathy, second, that this clubbing is identical with that found in hippocratic fingers except perhaps in the degree of development, third, that hippocratic fingers and osteo-arthropathy are associated with the same general group of diseases, and fourth, that twelve of the series of thirty-nine cases of simple clubbing examined by the Roentgen ray showed osseous changes in certain of the long bones of precisely the same type as found in osteo-arthropathy, it follows that the two conditions should be regarded as but different stages of the same disease.

## CONCLUSIONS

1. The evidence is overwhelming that hypertrophic osteo-arthropathy is always a secondary disease.

2. Among the primary diseases, pulmonary tuberculosis is probably the most important though rarely inducing the extreme degree of bone and joint changes seen with bronchiectasis.

3. There is a very definite correspondence between the characteristic clinical course of the disease and the process in the bones. During the periods of exacerbation in the primary disease, the pain, tenderness and swelling in the soft parts are not only increased, but the process in the bones is also more active. On the other hand, during the quiescent periods associated with cure or relief of the condition responsible for the bone and joint changes, the process in the bones is stationary and in rare instances actual resorption takes place.

4. The new subperiosteal bone, which is at first sharply marked off from the old shaft, later becomes (usually after a period of some

years) a more compact, dense layer, closely fused with the underlying old bone.

5. In the late stages of the most progressive type of cases there is evidence of wide-spread halisteresis in the affected long bones.

6. Occasionally the process in the bones and joints once established may progress even after actual cure of the primary disease.

7. The ungual phalanges as a rule show proliferative changes. They consist mainly in an irregular burr-like expansion of the distal half. More rarely small osteophytes are found at the proximal ends near the line of the joint cartilage.

8. The epiphyses of the affected long bones are to some extent always involved, but the new osseous tissue is much more irregular in outline and the ossification is less complete.

9. The proliferation in the long bones in advanced cases is more general than has been recognized, often affecting nearly the entire skeleton.

10. Changes in the joints are a constant and important feature of the disease. While the early changes are confined largely to the periarticular tissues, in the later stages, erosion of the cartilage, lipping about the joint, and even a moderate degree of ankylosis are common lesions.

11. A considerable percentage of cases of so-called hippocratic fingers show by means of skiagrams early proliferative changes in the periosteum of some of the long bones of the forearms and lower legs of exactly the same type as seen in hypertrophic osteo-arthropathy.

12. Simple clubbing of the fingers and secondary hypertrophic osteo-arthropathy should be considered as identical, the former representing an early stage of the latter.

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# CHRONIC ULCERATIVE COLITIS WITH POLYPS

## A CONSIDERATION OF THE SO-CALLED COLITIS POLYPOSA (VIRCHOW)*

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The finding of excrescences and polypoid projections of the mucosa in various parts of the alimentary tract is a comparatively frequent occurrence in the post-mortem room. The association of these with inflammation of the intestines, or at least a clinical history of dysentery, while not so frequent, has, nevertheless, been noted and described in the literature for a considerable time.

In 1721 Menzel[1] described a case in which there was a general inflammation of the intestinal tract and in the colon there were a number of wart-like excrescences. He presents with his report a crude etching of about 7 inches of the colon (Fig. 1). On it there are fifteen polypoid projections. The specimen was removed from a soldier who died of chronic dysentery.

In 1832 Wagner[2] in his description of the manner of healing of dysenteric ulcers noted that sometimes on the margins of the scars and on the healed surface of the smooth cicatrix of the healed ulcers tiny polypoid excrescences were found.

In 1839 Rokitansky[3] confirmed this observation of Wagner's and added that these small excrescences had their origin from islands of the mucous membrane that remained after the ulcerative process had ceased. He, moreover, does not limit the size of the projections. Later,[4] in describing the process of cicatrization of follicular and other ulcers of the colon he described the formation of polypoid growths from the ragged margins of ulcers.

Other systematic writers on pathological anatomy of this period, as Bock[5] among the German, Habershon,[6] Wilkes and Moxon[7] among the

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1. Menzel: Acta Medicorum Berlinensium, 1721, ix, 78.
2. Wagner: Med. Jahrb. d. k. k. ost. Staates, 1832, xi, 274.
3. Rokitansky: Med. Jahrb. d. k. k. ost. Staates, 1939, xxix, 88; also a Manual of Pathological Anatomy, London, 1849, ii, 86.
4. Rokitansky: Lehrbuch der path. Anatomie, Ed. 3, revised, Wien., 1861, iii, 209.
5. Bock: Lehrbuch der path. Anatomie, Ed. 4, Leipsic, 1864, p. 420.
6. Habershon: Diseases of the Abdomen, Ed. 2, London, 1862, p. 384.
7. Wilkes and Moxon: Lectures on Pathological Anatomy, Ed. 2, London, 1875, p. 416.

English, copied Rokitansky's descriptions, but added no specific observations.

In 1861 Lebert[8] reported the case of a woman, 32 years of age, who had suffered for years from an obstinate diarrhea. At section the mucous membrane of the colon was found beset with hundreds of little polypi, varying in size from a lentil to a bean, some pedunculated, others sessile. He described these polyps as consisting of fibrous tissue containing ramifying blood-vessels, but no glands. Glandular tubules were, however, to be found surrounding the base of the polyps. These tubules appeared normal.

In the same year Luschka[9] described a colon containing on its mucosa thousands of polyps. These varied in size from a hemp-seed to a bean and covered the mucosa from the ileo-cecal valve to the anus. On microscopic examination these polyps were found to consist of glands resembling the glands of Lieberkühn, except that they were longer, many of them more or less branched, and some of them dilated

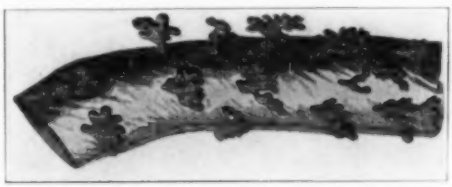

Fig. 1.—A photograph of the etching accompanying Menzel's report. If we compare this with the photograph of the colon from our first case, Figure 3, remembering that the dark areas in both pictures are the ragged tags of mucosa and submucosa, we see that the condition in the two colons must have been practically identical.

into cyst-like spaces. The mucous membrane between the glands was not markedly changed. The patient was a woman 30 years of age. She had for years suffered from a bloody diarrhea.

These last two cases, together with Menzel's, Virchow[10] has given as examples of a condition of the colon which he has called colitis polyposa. To these he has added one case. It was that of a boy 15 years of age who had died of dysentery. The polyps in this case were of the nature of vesicular, fluctuating prominences (Fig. 2). Many of them had scattered over their surfaces small openings from which gelatinous material protruded and could be expressed. Similar material was to be found in the mucosa between the polyps. On microscopic examination these vesicles were found to be dilated crypts of

8. Lebert: Traité d'anatomie path., Paris, 1861, ii, 316.
9. Luschka: Virchow's Arch. f. path. Anat., 1861, xx, 133.
10. Virchow: Die krankhaften Geschwülste, Berlin, 1863, i, 243.

Lieberkühn filled with mucous material. To this condition Virchow gave the name colitis polyposa cystica.

In 1881 Woodward,[11] the author of the "Medical and Surgical History of the War of the Rebellion," described two specimens from a colon that was sent to the Museum of the Surgeon General's Office for preservation. The patient was a woman aged 44, who for seven months before death was afflicted with a severe bloody diarrhea. At autopsy the ileum for 4 inches above the ileocecal valve and the colon for its whole length appeared ulcerated and inflamed. In the lower part of the transverse colon there were to be seen single follicular ulcers. These became larger and more numerous in the upper part of the descending colon, till a point was reached at which the whole mucosa was occupied by a single ulcer on the base of which there were numerous islands of thickened and puckered, undestroyed mucous

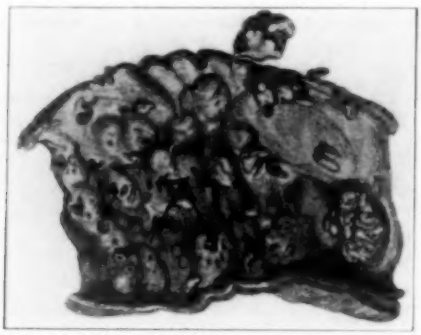

Fig. 2.—A copy of a portion of the colon from Virchow's case of colitis polyposa cystica. At "a" and "b" are to be seen open spaces. This suggests that secretions had accumulated in some of the spaces till they ruptured, which would represent a stage farther in this process than we have described.

membrane. The whole mucous surface of the lower portion of the descending colon was occupied by a single ulcer, projecting from the base of which were thirteen polypoid excrescences, some measuring as much as 14 mm. in length and 4 mm. in diameter. Some of the projections were more or less branched, but attached by a single pedicle like a genuine polyp; others were attached by double pedicles.

On microscopical examination the polyps were found to be composed of a central mass of connective tissue and a peripheral border of mucous membrane in a condition like that commonly found in chronic inflammation of the colon. The mucous membrane extended over the surface of the excrescence and its pedicle as far as its base, but was

11. Woodward: Am. Jour. Med. Sc., 1881, lxxxi, new series, p. 142.

absent from the surrounding flat surface of the intestine between the adjacent polyps. The intervening surface was composed of a vascular granulating tissue containing everywhere a large number of lymphoid cells. The glands of Lieberkühn over some of the polyps exhibited active hyperplasia.

The first case of this condition that came under our observation was necropsied at the Cleveland City Hospital about ten years ago. The patient was a woman about 36 years of age. About six months before entering the hospital she had given birth to a normal child. For a considerable time before admission she had been afflicted with a more or less severe diarrhea. Three months before admission this diarrhea had become a dysentery of a very annoying and exhausting character. She was in the hospital only a few weeks when death ensued, apparently from inanition and exhaustion.

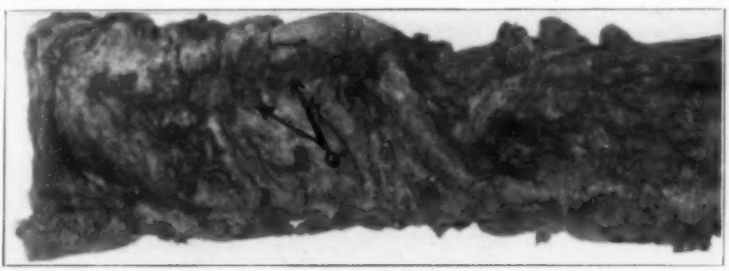

Fig. 3.—A portion of the colon from our first case. The ragged tags of mucosa and submucosa, as seen at "a," are the darker areas. The specimen having been preserved in alcohol had so faded that there was little contrast between the parts.

At the post-mortem examination the only lesion of importance found was in the colon. Here the entire mucous membrane from the ileocecal valve to the rectum was uniformly deeply ulcerated and existed as tags and localized islands (Fig. 3). The wall of the colon was moderately and generally thickened. In microscopic sections it was seen that the ulceration had extended through the submucosa to the muscularis (Fig. 4). The muscularis remained exposed and naked. Near its mucosal surface and extending into it there were numerous islands and columns of lymphocytes and polymorphonuclear leukocytes. There were also scattered eosinophils and plasma cells. The pedicle of the ragged tag of mucosa was composed of swollen and edematous submucosal tissue. In it were a number of blood-vessels, clusters and columns of lymphocytes and polymorphonuclear leukocytes with here and there scattered single eosinophils and plasma cells. The ragged tags were made up of mucosa and a portion of the attached

submucosa. The submucosal portion was everywhere infiltrated with leukocytes of the same character as those noted in the muscularis and pedicle. Large numbers of leukocytes were also seen in the mucosa between the tubules. The glands of Lieberkühn were everywhere more or less intact and there was no marked increase in the connective tissue between them. In certain places there was deposited between the tubules a brownish substance arranged in cell-like masses and in fine granular droplets. The peritoneum was slightly thickened and infiltrated with small round cells.

The following, our second observation, was more recent:

*Patient.*—A white man, aged 40, an American, an elevator man by occupation, was admitted to the Cleveland City Hospital July 26, 1913.

*History.*—His family history and personal history were unimportant. His present illness began with frequent stools two months before admission to the

Fig. 4.—A very low-power microscopic view of one of the tags of preserved mucosa and submucosa from our first case. It is to be noted here that there are no cystic spaces and the mucosa that remains is comparatively normal.

hospital. In spite of medical attention these had persisted and had recently been associated with great loss of weight and strength.

*Physical Examination.*—The patient was a well-developed but poorly nourished man. The skin was anemic, pale, yellow and dry. There were occasional râles to be heard over the chest and a soft systolic murmur along the left border of the sternum. No palpable masses were to be felt over the abdomen. On rectal examination a finger's length up the rectum a hard raised ring could be felt and all around it there were elevated masses. Blood and mucus came away readily with the finger as it was withdrawn. The blood-count on admission was, red blood cells, 4,048,000; white blood-cells, 6,600; hemoglobin, 50 per cent. Differential count, polymorphonuclear neutrophils, 63.5 per cent.; small mononuclears, 18.5 per cent.; large mononuclears, 7 per cent.; transitionals, 5 per cent.; eosinophils, 0.5 per cent.; mast cells, 0.5 per cent. There was fairly marked anisocytosis and poikilocytosis. A specimen of feces

examined on admission was of a reddish-brown color and of very foul odor. It gave a positive test for bile. Microscopically numerous red blood-cells were to be seen but no amebas parasites, or ova of parasites. The Wassermann reaction was negative. Examination of the urine gave, on admission, a faint trace of albumin. This soon disappeared, and thereafter the urine was negative for albumin, sugar and casts.

*Course.*—The patient was in the hospital a little over three months and three weeks. During this period the temperature was quite variable but never above 101. Generally it was normal or subnormal. The number of stools varied from one to four per day. The patient died in the hospital.

*Clinical Diagnosis.*—Carcinoma of rectum.

*Necropsy.*—Performed about six hours after death. Excepting a moderate parenchymatous degeneration of the heart muscle, liver and kidneys, and a peripheral fatty degeneration of the liver lobules, there were no lesions of importance to be noted outside of the alimentary tract.

The stomach, duodenum and jejunum presented nothing markedly abnormal.

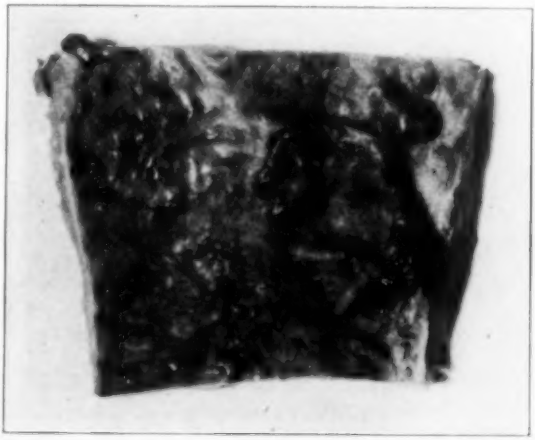

Fig. 5.—A cluster of polyps from our second case. At *a* and *b* are to be seen numerous small islands of mucosa and of submucosa.

The mucosa of the lower two-thirds of the ileum was injected, edematous, and its surface covered with a thin, grayish layer of exudate. At irregular intervals small areas of marked injection, as of beginning ulcers, were to be noted. In the lower portion of the ileum, near the ileocecal valve, and in the cecum there were single ulcers. These ulcers were of all sizes from a millimeter to a centimeter in diameter. The small ulcers were of a "punched-out" character and extended only through the mucous membrane. The larger ulcers were very irregular, with ragged margins and floor, and extended deeper into the intestinal wall. On the base of several of the largest ulcers there were attached islands and tags of mucosa and submucosa.

The appendix appeared normal and not to have been at all affected by the inflammatory process involving the cecum and ileum.

The wall of the colon was generally and moderately thickened, rather fibrous and stiffly flexible, though in some places it had been so eroded as to be thinner than normal. The intestine was generally contracted and its lumen narrowed. The mucosa of the ascending and transverse portion was covered

with a thin layer of grayish exudate. It was moderately injected and, over irregular areas, eroded to varying depths. Over the eroded areas were to be seen islands of deeply injected mucosa. Many of the small tufts of mucosa were attached by slender pedicles of submucosa and were easily removed by passing the finger over the surface. In the descending colon the mucosa was likewise injected and eroded. At a point about 8 cm. above the sigmoid flexure there were to be seen a few short polypous projections. These projections measured from 2 to 3 mm. in diameter. They were stubby and attached by a relatively thick pedicle. About the sigmoid flexures there was a cluster of fairly large and long polypous masses. One of these masses in particular had a long slender pedicle and a clubbed termination. It measured about 2.5 cm. in total length and the clubbed extremity 4 mm. in diameter at its widest part.

From the sigmoid flexure to about 12 cm. above the external sphincter of the anus polypous projections were more numerous and of various sizes and shapes. Some of the polyps were small sessile projections, measuring from 1 to 2 mm. in height and in diameter; others were irregular, 0.5 to 1.5 cm. in length and in diameter, attached by short slender pedicles — some of the

Fig. 6.—A copy of the drawing of a microscopic section of one of the polyps from Woodward's case. The central mass of connective tissue and the surrounding layer of preserved mucosa is well shown.

pedicles appearing so slender as to be scarcely strong enough to support the nodule on their ends (Fig. 5). In all, there were about forty polypous projections.

*Microscopic Examination.*—In microscopic sections of the lower portion of the ileum the mucous membrane was found to be swollen and edematous. Its surface was covered with a layer of mucus and detritus in which large numbers of leukocytes and glandular desquamated cells were to be seen. The connective tissue between the crypts and glands of Lieberkühn was moderately increased and infiltrated with polymorphonuclear leukocytes, lymphocytes and plasma cells. The blood-vessels were dilated and filled with blood. The submucosa and muscular layer were likewise swollen, edematous and infiltrated with leukocytes. The peritoneal layer was slightly swollen and infiltrated with leukocytes, but there was no exudate on its surface.

In sections of the single ulcers in the lower portion of the ileum and in the cecum there were seen to be areas of necrosis and ulceration, in some places extending no deeper than the mucosa; in other places, however, particularly in association with the larger ulcers, the necrosis extended through the sub-

mucosa to the muscularis. The margins of the ulcers were swollen, edematous and infiltrated with fibroblasts, large numbers of lymphocytes, polymorphonuclear leukocytes, eosinophils and plasma cells. Some of the margins were sloping and fairly smooth; others were deeply undermined, irregular and ragged. The floor of the ulcers, particularly the large ulcers, was, for the most part, smooth but irregular in outline. There were small elevations on the floor of many of them. These elevations were quite vascular. Some of them were covered with mucous glands; others contained only the fundi of the glands, while others were simple vascular tufts without covering.

The mucous surface of the colon everywhere presented the picture of a chronic inflammatory and ulcerative process with here and there areas and islands of granulation tissue. The surface was covered with a layer of necrosed tissue cells which extended to a variable depth from a few micromillimeters below the surface of the mucosa to several micromillimeters into the submucosa, even to the muscular layer. Beneath the layer of necrotic cells the glandular tubules, where present, were spread far apart by the proliferation of fibroblasts and the infiltration of lymphocytes and polymorphonuclear leukocytes, eosinophils and plasma cells. In most places only the bases of the crypts of Lieberkühn remained. In some places these had been overgrown by the

Fig. 7.—A very low power photomicrograph of a section of one of the polyps from our second case to show the dilated cystic spaces in the mucous layer. The dark line across the top represents a fold in the section.

fibroblasts and the accumulation of secretions had caused them to become dilated and to appear as small cysts. The blood-vessels and capillaries were dilated and congested. Scattered areas of hemorrhage were to be seen on the surface. The submucosa, where not eroded, was generally thickened and fibrous. Infiltrating it were a number of scattered areas of leukocytes, eosinophils and plasma cells. The solitary follicles were small and irregular in size and distribution. The muscular layers were moderately infiltrated with lymphocytes, leukocytes, eosinophils and plasma cells. The peritoneum appeared slightly thickened.

The sessile projections and polyps, noted in the descending colon and rectum, microscopically presented the same appearance as that described and pictured by Woodward in the case he described (Fig. 6). There was a central mass of connective tissue which formed the base and support of the polyp. The central connective tissue mass was surrounded by an irregular, rather thick, layer of glandular acini and tubules. The connective tissue extended between the tubules and had in places contracted and occluded them, causing a retention of secretions of the glands and cyst-like dilatations (Fig. 7). The structures were quite vascular and everywhere infiltrated with lymphocytes, polymorphonuclear leukocytes, eosinophils, plasma cells and large epithelioid cells

The mucosae around the bases and pedicles were for the most part absent, or represented only by scattered fundi of crypts imbedded in fibrous tissue. They were very vascular. The blood-vessels were dilated and engorged with blood. Many of the smaller tufts were made up entirely of collections of budding blood-vessels, fibroblasts, and leukocytes without mucous crypts or glands.

The islands and tags of mucosa and submucosa that had been the source of the polyp formation appeared to depend for their preservation on the blood-vascular arrangement; for it was to be noted that the polyps in the rectum were situated along the side of the intestinal wall, while higher up and in the colon the polyps were situated along the line of attachment of the mesentery, an arrangement that coincides with the blood-supply of the parts. The blood-supply of these small and localized areas appeared to have been sufficient to withstand the destructive action of the inflammatory process, so that necrosis did not take place. The coincident increased blood-supply did, however, produce active hyperplasia of the mucous glands and the submucous connective tissue, with consequent polyp-like formations, as described by Rokitansky. The increased and proliferated fibrous tissue on contracting had caused an occlusion of many of the tubules and retentions of their secretions had caused cyst-like formations, as described by Virchow. Probably, as Virchow has suggested, the formation and lengthening of the pedicles of the polyps had been aided by the active peristalsis and the passing of the feces over the surface of the polyp. Our second specimen, like Luschka's, was not cystic, but cyst-like spaces were present over the mucous surface of the colon between the polyps and over the surfaces of the polyps (Fig. 7).

It appears very probable that the two cases which we have here presented represent, respectively, a very early and a comparatively late stage in this particular condition of the colon designated by Virchow as colitis polyposa. If so, they, with the cases reported in the literature, aid us materially in working out the natural pathological history of the lesions of this affection and of ulcers of the alimentary tract.

There appears in the beginning of this disease to be a general colitis, producing a number of local undermining ulcers similar to those found in our second case in the cecum and in the lower portion of the ileum, near the ileocecal valve. Clinically, there is associated with the lesions at this stage a moderate diarrhea. The ulcers tend to increase in number and in size till nearly the whole mucous surface of the colon is involved. Clinically, during this period there is an increase in the number and a change in the character of the stools. The ulcers as they increase in size fuse and form large irregular ulcerated areas, similar to those presented in our first specimen (Fig. 3). The ulcerative process, though severe and chronic, is of such a character that portions

of the mucosa and submucosa adjacent to and supplied, apparently, by the primary arterial branches is preserved. These portions of the mucosa and submucosa remain as ragged tags scattered over the surface of the colon. As the process ameliorates and healing begins the irregular margins of these tags become smoothed off and remain as rounded sessile elevations or as polypoid projections of the mucous surface. The portions of the mucosa that remain in these areas regenerate over the surface, around the base or pedicle and, if conditions remain favorable, ultimately, over the barren and denuded submucosa and together with submucosa over the muscular layer. The mucosa may thus be completely restored, and, with its numerous scattered polypous projections, present a perfect picture of colitis polyposa. Coincident with the process of healing, and later, the proliferated fibroblasts begin to contract, as in the cicatrization of a wound. This leads to an occlusion of the orifices of certain of the tubules situated in the polyps and over the mucosa between the polyps. There is then an accumulation of secretions in these occluded tubules with the ultimate formation of retention cysts. These of course increase in size as long as there are secreting cells in their walls, and as there are a greater number of tubules over the surface of the polyp than over the surface of the mucosa, the polyp may appear as a collection of small cysts. It is probably in this manner, as before stated, that the condition which Virchow has designated as colitis polyposa cystica is brought about. It is the end stage of colitis polyposa.

# OBSERVATIONS ON THE USE OF THE ABDERHALDEN REACTION WITH NORMAL AND PATHOLOGICAL HUMAN SERUMS *

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The material of this paper is arranged in the following order:

1. Negative reactions with testicular substrate and male dementia praecox serum.

2. A comparison between the blood-serum of normal persons and those suffering with general paralysis of the insane as regards proteolytic action on brain substrates at various stages of washing.

3. Proteolysis of substances precipitated from the water used for washing various organs in the course of preparing substrates.

4. Comparison of the proteolysis of emulsions, prepared by concentrating the washings from brain substrate, by serum from general paralysis and normal persons.

In a previous communication[1] we proved, first, that the serums of normal animals contain ferments capable of giving positive Abderhalden reactions with substrates prepared from many body tissues, and second, that the substance (or substances) which gives the reaction may be removed from the substrates if the washing[2] with acidified water is continued long enough. This work was done on dogs and cats. The results to be reported here were obtained with human serums and substrates.

First, it was demonstrated that normal human blood serum contains ferments capable of digesting brain tissue substrate at a certain stage in the process of washing, when it no longer gives any ninhydrin reaction without previous lysis. It was also demonstrated that the washings contain a substance capable of digestion by normal serum. As these results will be used for the demonstration of certain other points in comparison with pathologic serums, the tabulation for the moment will be postponed.

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* Submitted for publication Nov. 12, 1914.
* From the laboratory of the Illinois State Psychopathic Institute.
* Read before the Mississippi Valley Medical Association, Oct. 29, 1914.

1. Ross, E. L., and Singer, H. D.: A Point to be Considered in the Use of the Abderhalden Reaction, THE ARCHIVES INT. MED., 1914, xiv, 552.

2. It should be stated that this refers to the washing by boiling after the tissues have been thoroughly freed from blood by washing in cold water, as recommended by Abderhalden.

### REACTIONS BETWEEN DEMENTIA PRAECOX SERUM AND SEX-GLAND SUBSTRATE

As our work demands a special interest in the problems of psychiatry we have performed a series of tests on the digestion of substrates prepared from testes with the serum of male patients presenting a dementia praecox picture. The available supply of this tissue was necessarily small, hence all was composited and it was then washed twenty times. The series of blood-serums employed for testing with this material comprised seventeen cases of undoubted dementia praecox type, and all, with one exception, gave an entirely negative result. One serum was recorded as doubtful, there being a mere suspicion of a blue color on boiling with ninhydrin. It thus seemed clear that sufficient washing of the substrate will cause a negative reaction between the blood-serum of these individuals and testicular tissue.

It is therefore justifiable to insist, as was done in our previous communication[1] that a positive Abderhalden reaction with sex-gland means nothing at all unless it is demonstrated to be stronger than that obtained with a sample of the identical (not merely similar) substrate and a series of normal serums.

### REACTIONS OF GENERAL PARALYTIC AND NORMAL SERUMS WITH BRAIN SUBSTRATES

Sex-glands are so small that it is impossible, without a prolonged wait, to use them for a series of studies. In paresis, however, we have an excellent example of a disease in which an organ, the brain, is undergoing destruction and alteration from its normal structure and composition. According to Abderhalden's theory of the development of protective ferments, the serums of paretics should certainly contain enzymes capable of digesting brain protein. Therefore, as these materials were readily obtainable, it was decided to work with brain substrate and paretic serums.

In the light of our previous results, the washing of the brain tissue was made a prominent factor in the investigation. Each brain was washed twelve to fourteen times. At different stages of this washing quantities of the tissue were taken out and saved as an individual substrate. Thus, from each brain, three or four substrates were prepared.

*Source of Material.*—Since it has not yet been determined whether it is permissible to use pathological material for substrates, it seems well to specify the source of the material employed.

*Brain 1* was obtained five hours after death, from a white man 24 years of age, who died seven hours after an injury to the head which had given rise to a hemorrhage at the base of the brain in the region of the right carotid artery. From the history obtained, this

man had always been healthy, did not take alcoholic beverages and had had no venereal infection. No evidence of disease was found anywhere in the body either macroscopically or microscopically.

*Brain 2* was removed twelve hours after death, from the body of a white man 42 years of age. This man had been epileptic for thirty years and was considerably demented. Death took place in a condition of status epilepticus and the autopsy revealed engorgement of

TABLE 1.—ABDERHALDEN TESTS WITH SERUM OF PARETICS AND BRAIN PROTEIN

| Donor of Serum | Source of Substrate | Results at Different Stages of Washing. Substrate Boiled with Acidified Water | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 2 Times | 3 Times | 5 Times | 8 Times | 10 Times | 11 Times | 13 Times | 14 Times | 15 Times |
| A. C. ..... | Brain 1 | .... | ++ | .... | + | .... | .... | — | .... | .... |
| A. B. ..... | Brain 1 | .... | ++ | .... | + | .... | .... | — | .... | .... |
| L. C. ..... | Brain 1 | .... | ++ | .... | +(?) | .... | .... | — | .... | .... |
| C. S. ..... | Brain 1 | .... | + | .... | — | .... | .... | — | .... | .... |
| E. M. ..... | Brain 1 | .... | + | .... | — | .... | .... | — | .... | .... |
| D. M. ..... | Brain 1 | .... | + | .... | — | .... | .... | — | .... | .... |
| A. C. ..... | Brain 2 | .... | .... | .... | .... | .... | .... | .... | .... | — |
| A. B. ..... | Brain 2 | .... | .... | .... | .... | .... | .... | .... | .... | — |
| L. C. ..... | Brain 2 | .... | .... | .... | .... | .... | .... | .... | .... | — |
| F. F. ..... | Brain 2 | +++ | .... | ++ | .... | + | .... | .... | .... | — |
| W. B. ..... | Brain 2 | +++ | .... | ++ | .... | — | .... | .... | .... | — |
| E. J. ..... | Brain 2 | .... | .... | ++ | .... | — | .... | .... | .... | — |
| J. H. ..... | Brain 3 | +++ | .... | ++ | + | .... | + | .... | — | .... |
| W. B. ..... | Brain 3 | ++ | .... | + | +(?) | .... | + | .... | — | .... |
| W. L. ..... | Brain 3 | ++ | .... | ++ | + | .... | — | .... | — | .... |
| L. C. ..... | Brain 3 | + | .... | + | — | .... | — | .... | — | .... |
| T. G. ..... | Brain 3 | + | .... | + | — | .... | — | .... | — | .... |
| A. B. ..... | Brain 3 | + | .... | — | — | .... | — | .... | — | .... |
| A. C. ..... | Brain 3 | + | .... | — | — | .... | — | .... | — | .... |
| E. J. ..... | Brain 3 | + | .... | — | — | .... | — | .... | — | .... |
| Total positives possible | | 30 | 18 | 33 | 42 | 9 | 24 | 18 | 24 | 18 |
| Actual positives obtained..... | | 18 | 9 | 13 | 6 | 1 | 2 | 0 | 0 | 0 |
| Percentage of positives | | 60.0 | 50.0 | 39.4 | 14.3 | 11.1 | 8.3 | 0.0 | 0.0 | 0.0 |

TABLE 2.—ABDERHALDEN TEST WITH SERUM OF NORMAL PERSONS AND BRAIN PROTEIN

| Donor of Serum | Source of Substrate | Results at Different Stages of Washing. Substrate Boiled with Acidified Water | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 2 Times | 3 Times | 5 Times | 8 Times | 10 Times | 11 Times | 13 Times | 14 Times | 15 Times |
| T. B. | Brain 1 | .... | +(?) | .... | — | .... | .... | — | .... | .... |
| E. R. | Brain 1 | .... | — | .... | — | .... | .... | — | .... | .... |
| R. M. | Brain 1 | .... | — | .... | — | .... | .... | — | .... | .... |
| H. S. | Brain 1 | .... | — | .... | — | .... | .... | — | .... | .... |
| E. R. | Brain 2 | ++ | .... | .... | .... | .... | .... | .... | .... | — |
| T. B. | Brain 2 | ++ | .... | — | .... | — | .... | .... | .... | — |
| R. M. | Brain 2 | ++ | .... | — | .... | — | .... | .... | .... | — |
| H. S. | Brain 2 | +++ | .... | — | .... | — | .... | .... | .... | — |
| H. S. | Brain 3 | + | .... | — | — | .... | — | .... | — | .... |
| C. N. | Brain 3 | + | .... | — | — | .... | — | .... | — | .... |
| E. F. | Brain 3 | + | .... | — | — | .... | — | .... | — | .... |
| E. R. | Brain 3 | + | .... | — | — | .... | — | .... | — | .... |
| Total positives possible | | 24 | 12 | 21 | 24 | 9 | 12 | 12 | 12 | 12 |
| Actual positives obtained | | 13 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Percentage of positives | | 54.2 | 8.3 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |

cerebral vessels, an old hemorrhagic cyst in the left hippocampus, healed tuberculosis of lungs and cholelithiasis with chronic inflammation of the liver and splenic capsules.

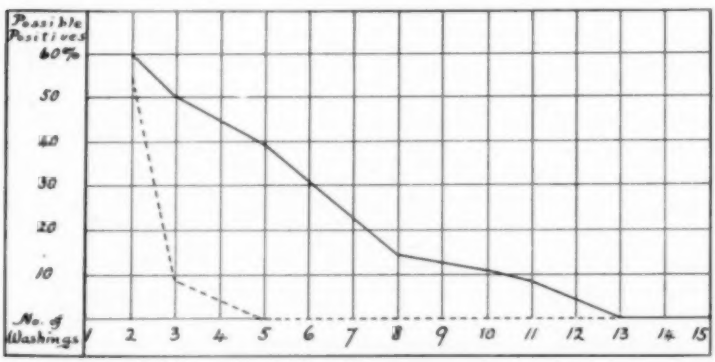
*Brain 3,* removed twenty hours after death from the body of a white woman, aged 61. The woman had presented a picture of a paranoid type of dementia praecox for more than twenty years. Death resulted from a subacute ulcerative colitis with an abscess in the left lung. There was much fatty degeneration of the myocardium and liver and some cloudy exudate beneath the pia mater.

Brain 1 may be considered as an ideal specimen for the purpose, whereas Brains 2 and 3 are both of questionable value. Nevertheless, the results in all three are so similar that it has been deemed justifiable to combine them for the purpose of drawing conclusions.

A series of tests with paretic and normal serums was made on each brain series. The results are given in Tables 1 and 2.

The curves shown in the chart are constructed from the data of Tables 1 and 2. The horizontal distances represent the number of washings while the vertical distances indicate the proportion, in percentage, of the actual number of positives obtained to the number possible, allowing + + + as a complete reaction.

It is evident from these results that the ferment activity of the serum of paretics differs from that of normal persons. Even with the fewest number of washings the substrate was slightly less digested by normal serums. The third washing seemed to have caused the greatest difference in the digestibility of the tissue by the two classes of serum. No digestion of the brain occurred with normal serum after it had been washed five times, while there was considerable digestion with paretic serum till the thirteenth washing was reached. This is capable of various explanations.




Proteolysis of brain substrates at different stages of washing by serums from normal persons and cases of general paralysis. General paralysis serum, solid line; normal serum, broken line.

The first possibility which occurred to us was that the substrate might contain originally at least two classes of proteins, one easily washed out with acidified water, the other requiring more prolonged washing. If, then, the serum of paretics contained two kinds of ferment, one of which was common to all human blood-serum and caused lysis of the easily removable protein, while the other was specific in the sense that it was produced in response to the absorption of dead brain tissue resulting from the disease, paresis, and which acted on that class of proteins less easily washed out, the main facts established by these tests would be intelligible. Such a view is not out of harmony with Abderhalden's theory of protective ferments, although it brings in other factors not hitherto considered.

This would readily explain the abrupt fall in the curve showing the digestion of brain substrate by normal serums after the second boiling, and would permit an understanding of the digestion of substrates from various organs by normal serums. Nevertheless, it seemed also necessary to consider a simpler explanation, at variance with the more generally accepted views, which is to the effect that there may be in brain substance a class of proteins capable of being washed out by boiling with acidified water and at the same time of being digested by a ferment (or ferments) present in both normal

TABLE 3.—EFFECT OF VARIATIONS IN QUANTITY OF SERUM USED*

| Donor of Serum | Quantity of Serum, c.c. | Results on Brain 1 when Boiled | | |
|---|---|---|---|---|
| | | 2 Times | 5 Times | 8 Times |
| Paretics— | | | | |
| L. C. | 0.5 | — | .. | .. |
| F. G. | 0.5 | — | .. | .. |
| A. B. | 0.5 | — | .. | .. |
| A. C. | 0.5 | — | .. | .. |
| E. J. | 0.5 | — | .. | .. |
| L. C. | 1.0 | + | + | — |
| F. G. | 1.0 | + | + | — |
| A. B. | 1.0 | + | — | — |
| A. C. | 1.0 | + | — | — |
| E. J. | 1.0 | + | — | — |
| L. C. | 1.5 | + | — | — |
| F. G. | 1.5 | +++ | .. | .. |
| A. C. | 1.5 | +++ | .. | .. |
| E. J. | 1.5 | +++ | .. | .. |
| Normals— | | | | |
| H. S. | 1.0 | + | — | — |
| C. N. | 1.0 | + | — | — |
| A. F. | 1.0 | + | — | — |
| E. R. | 1.0 | + | — | — |
| E. R. | 1.5 | ++ | + | + |

* It should be noted that control tests with substrate alone and with serum alone in similar quantities were used in each instance and proved uniformly negative.

and paretic serum, but that the conditions for enzyme activity are more favorable, for some reason, in paretic than in normal serum.

To test this latter hypothesis a series of reactions was made on brain substrates with varying amounts of serum. The results are given in Table 3.

From these results it is obvious that the quantity of serum used materially affects the degree of proteolysis which occurs, and hence that it is permissible to consider quantity as well as quality of ferment as a factor in determining the results of the test.

### REACTIONS WITH NORMAL SERUMS AND PRECIPITATES FROM WASHINGS OF SUBSTRATES

In a previous paper we showed that a material which gave a positive Abderhalden reaction with normal animal serums could be precipitated with alcohol from the water used for washing in the preparation of animal substrates. Similar preparations were made from human tissues. The results of reactions with these precipitates are given in Table 4.

TABLE 4.—ABDERHALDEN TESTS WITH NORMAL SERUM AND SUBSTANCES PRECIPITATED FROM TISSUE WASHINGS

| Donor of Serum | Substrate | Result |
|---|---|---|
| H. S. | Thyroid preparation | + |
| H. S. | Spleen | − |
| H. S. | Testes | ++ |
| H. S. * | Placenta | ++ |
| E. R. | Suprarenal | ++ |
| E. R. | Brain | + |
| E. R. | Liver | − |
| E. R. | Kidney | ++ |

* Male.

From Table 4 it will be observed that positive reactions were obtained with precipitates from the washings of all organs tested, with the exception of liver and spleen. It is of especial importance to note that a strong positive was obtained with a normal male serum and the precipitate from placental washings. These results, and especially that with the placental preparation, suggest that there is some one protein (or group of proteins) common to most tissues which is capable of lysis by ferments normally present in the blood-serum.

PROTEOLYSIS OF EMULSIONS OBTAINED FROM WATER USED FOR WASHING SUBSTRATES ALREADY NEGATIVE TO NORMAL SERUMS

It will be noticed in Table 2 that no normal serum tested gave a positive reaction with substrate which had been washed five or more times, and in Table 1 that the number and degree of positive reactions with the use of paretic serums gradually diminished as the washing was continued, until they finally disappeared entirely. It thus seemed possible that an examination of the fluid used for washings later than the fifth might throw some light on the relation of the material washed out of the substrate at this stage to the ferments present in normal and paretic serums. For it seems clear that all the protein capable of

TABLE 5.—ABDERHALDEN TEST WITH AN EMULSION PREPARED BY CONCENTRATING THE WATER USED FOR THE FIFTH TO EIGHTH WASHINGS OF BRAIN SUBSTRATE, INCLUSIVE

| Donor of Serum | Quantity of Emulsion | | | | |
|---|---|---|---|---|---|
| | 3 c.c. | 1 c.c. | 0.5* c.c. | 0.2* c.c. | 0.1* c.c. |
| Paretics— | | | | | |
| L. C. | + | .. | .. | .. | .. |
| F. G. | +++ | .. | .. | .. | .. |
| A. C. | +++ | .. | .. | .. | .. |
| E. J. | +++ | .. | .. | .. | .. |
| H. M. | .. | + | — | — | — |
| E. M. | .. | ++ | — | — | — |
| E. P. | .. | ++ | — | — | — |
| Normals— | | | | | |
| H. S. | .. | ++ | ++ | — | — |
| H. C. | .. | + | — | — | — |
| E. R. | .. | + | +? | — | — |

* The bulk was made up to 1 c.c. by the addition of distilled water.

cleavage by protective enzymes present in blood-serum is gradually removed, and hence that if there be two kinds of such proteins and two kinds of ferment, as in the hypothesis advanced above, those washings made after the substrate has become negative to normal serum, will contain only, or almost alone, the substance more difficult of removal, and, according to the hypothesis, capable of digestion only by a ferment specific for paretic serum. In such case the material precipitated from these later washings should give a negative reaction with normal serum and a positive with paretic serum, or at least the reaction should be more marked with the latter than with the former.

For this purpose the fifth, sixth, seventh and eighth washings were compounded and were concentrated to an emulsion by heating on a steam bath. As nothing was known of the amount of this emulsion to be used for a test, varying amounts were employed with 1 c.c. of serum from both paretic and normal persons. Control tests with emulsion alone and serum alone were negative throughout. The results of the tests are given in Table 5.

These results demonstrate that the material which was washed out, even after the substrate had ceased to give a positive reaction with normal serum, was still as readily digested by normal as by paretic serum, and consequently point strongly to the conclusion that the continued positive reaction with paretic serums is due to some factor which favors enzyme activity in these as compared with normal serums. This might be expressed by saying that the difference is quantitative rather than qualitative.

## SUMMARY

1. Substrates prepared from certain human tissues contain material which is digested by ferments present in normal human serum.

2. This material can be washed out by boiling repeatedly with slightly acidified water.

3. The water used for washing contains material which can be digested by normal serum ferment.

4. Brain substrate which has been washed until it no longer gives positive reactions with normal serum may still be digested by the serum of general paralytics.

5. The material which undergoes lysis from the action of ferments in the serum of general paralytics can be removed by further washing.

6. The material removed by washing after the substrate has become negative to normal serum is digested by the ferments of normal serum in as great a degree as by that of general paralysis.

## CONCLUSIONS

The published results of experiments on the lysis of tissue substrates by various pathological serums are of no value in permitting conclusions as to the seat of the lesion.

The difference in ferment activity on brain substrates between the serum from general paralysis and that from normal persons appears to be quantitative rather than qualitative.

# THE FACTORS OF COAGULATION IN PRIMARY PERNICIOUS ANEMIA *

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Within the past two years it has become more and more possible to study the factors concerned in blood coagulation. The literature of this period has even given promise of an etiological classification of hemorrhagic disease, but developments have not borne out this promise. If we accept the theory of Howell,[1] there are five factors in coagulation — antithrombin, thromboplastin, calcium salts, prothrombin and fibrinogen — which may show variations in disease. Antithrombin, prothrombin, calcium salts and fibrinogen are present in the circulating blood. The prothrombin, however, is held in combination with antithrombin and thus prevented from activation into thrombin by calcium. Without thrombin there can be no coagulation. The presence of thrombin is secured through the fixation or neutralization of antithrombin by thromboplastin. This last substance, thromboplastin, frees the blood of antithrombin; under these conditions calcium at once forms thrombin from prothrombin; thrombin reacts with fibrinogen and gives fibrin.

If, on the other hand, we accept the theory of Morawitz, with which most other theories can be brought into accord, we have four possible factors to consider. The existence of antithrombin is admitted by this investigator, but it is not regarded as an essential part of the process. According to Morawitz, thrombokinase (Howell's thromboplastin) transforms thrombogen — normally circulating in the blood — to prothrombin; prothrombin later is converted into thrombin by calcium salts. Thrombin reacts with fibrinogen and gives fibrin. It is not possible to differentiate thrombogen and prothrombin so that the latter alone represents this factor in our experiments.

## QUANTITATION OF THE COAGULATION FACTORS AND THEIR VARIATIONS IN DISEASE

1. *Antithrombin.*—Howell[2] has given us a rapid method for preparing thrombin. Making use of this thrombin and of a normal salt

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* From the Peter Bent Brigham Hospital, Boston.

1. Howell, W. H.: The Rôle of Antithrombin and Thromboplastin (Thromboplastic Substance) in the Coagulation of the Blood, Am. Jour. Physiol., 1911, xxix, 187.

2. Howell, W. H.: Rapid Method of Preparing Thrombin, Am. Jour Physiol., 1913, xxxii, 264.

solution of dried oxalated plasma, which contains active fibrinogen, he has shown that we may get coagulation in from three to ten minutes. Such a system can be rendered non-coagulable, or coagulation can be greatly delayed by the addition of oxalated plasma which has been heated to 60 C. This prevention of coagulation is ascribed to the antithrombin present normally in the blood, and on this basis one may readily test the antithrombin in different clinical conditions. Our technic for these determinations has been that described by Howell[3] and is illustrated in the protocol which follows. Making use of this method, Howell[3] has shown a diminution of antithrombin in three cases of thrombosis; Whipple[4, 5] an increase in one case of profound septicemia; in a case of typhoid fever with complicating liver disease; in a case of miliary tuberculosis with epistaxis; in a case of generalized thrombosis; in a case of leukemia with purpura; in a case of aplastic anemia with purpura and hemorrhage from the nose and gums. These are diverse conditions, and the method of taking the blood has not been uniform. In many of his determinations Whipple used blood from the heart collected some time after death, and his controls in antithrombin have not been as complete as Howell's present methods seem to us to require. Austin and Pepper[6] found an increase in antithrombin in one case of simple purpura.

2. *Thromboplastin (thrombokinase of Morawitz).*—Thromboplastin can be shown to be present in blood in many ways, but for quantitation there is at present no better method than the platelet count. It must be noted, however, that all the formed elements of the blood have been shown to have thromboplastic properties and that the platelets have also been shown to contain prothrombin,[7] so that by this count we do not accomplish our purpose either completely or exactly. The literature on the platelets is large, and it suffices to say that they have been shown to be increased in pneumonia, post-hemorrhagic anemia, and myeloid leukemia; in short, in diseases leading to multiplication of bone-marrow cells. They are decreased in most cases of pernicious anemia, in lymphatic leukemia, in typhoid and many other fevers, and in purpura hemorrhagica, whether primary or secondary. With the

3. Howell, W. H.: The Condition of the Blood in Hemophilia, Thrombosis and Purpura, THE ARCHIVES INT. MED., 1914, xiii, 76.

4. Whipple, G. H.: Hemorrhagic Disease — Septicemia, Melena Neonatorum and Hepatic Cirrhosis, THE ARCHIVES INT. MED., 1912, ix, 365.

5. Whipple, G. H.: Hemorrhagic Disease. Antithrombin and Prothrombin Factors. THE ARCHIVES INT. MED., 1913, xii, 637.

6. Austin, J. H., and Pepper, O. H. P.: Experimental Observations on the Coagulation of Oxalated Plasma, with a Study of Some Cases of Purpura, THE ARCHIVES INT. MED., 1913, xi, 305.

7. Morawitz, P.: Beiträge sur Kenntniss der Blutgerinnung, Deutsch. Arch. f. klin. Med., 1904, lxxix, 215; Baynes-Jones, S.: The Presence of Prothrombin and Thromboplastin in the Blood Platelets, Am. Jour. Physiol., 1912, xxx, 74.

exception of one observation by Austin and Pepper[6] we know of no cases of hemophilia in which they have been found deficient. Sahli[8] and Morawitz and Lossen[9] ascribe hemophilia to defective formation of thromboplastic material by injured vessel walls. This opinion is arrived at by a process of exclusion of other factors, but not by direct experiment.

3. *Calcium.*—The third factor in the coagulation system, calcium, has not been studied in our series of cases. Wright[10] has advocated the treatment of hemophilia by administration of calcium, and the weight of his advice has led to the indiscriminate use of calcium salts in bleeding conditions. Nolf[11] has absolutely denied calcium diminution in hemophilia, and it appears probable that this factor may be neglected in hemorrhagic disease.

4. *Prothrombin.*—This cannot be determined with entire certainty. If one takes oxalated plasma and to a series of tubes adds dilute calcium chlorid, coagulation will result and the coagulation time will be shortest in the tube which happens to receive the optimum amount of the salt. Howell[3] has held that this is a quantitative test for prothrombin, and making use of it he has shown a great prolongation of coagulation time (on recalcification) in three cases of hemophilia, and he therefore ascribes the disease to a prothrombin deficiency. We believe the test most useful, but think it should be subjected to certain precautions. Lee and Vincent,[12] using human blood, have shown that the time of coagulation of recalcified oxalated plasma varies directly with the length of time of centrifugalization and they have felt that this is due to removal of formed elements. Perfectly clear plasma, the result of prolonged high-speed centrifugalization, clots in forty-five minutes on recalcification; cloudy plasma poorly centrifugalized in fifteen minutes at most. It seems proved, therefore, that the speed of Howell's prothrombin reaction can be modified by centrifugalization, and it is probable that this is due to alterations in the solid content of the plasma. Since each prothrombin test must be controlled by a similar test on normal plasma it becomes of prime importance that the test and control material be similarly treated.

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8. Sahli, H.: Ueber das Wesen der Hämophilie, Ztschr. f. klin. Med., 1905, lvi, 264.

9. Morawitz, P., and Lossen, J.: Ueber Hämophilie, Deutsch. Arch. f. klin. Med., 1908, xciv, 110.

10. Wright, A. E.: Remarks on Methods of Increasing and Diminishing the Coagulability of the Blood, with Especial Reference to Their Therapeutic Employment, Brit. Med. Jour., 1894, ii, 57.

11. Nolf, P.: Eine Neue Theorie der Blutgerinnung, Ergebn. d. inn. Med. u. Kinderh., 1913, x, 275.

12. Lee, R. I., and Vincent, Beth: The Coagulation of Normal Human Blood, The Archives Int. Med., 1914, xiii, 398.

Without mentioning the use of such precautions, Whipple[4, 5] has reported two cases of melena neonatorum with diminished prothrombin. Addis[13] also believes that a diminution of prothrombin is the cause of hemophilia.

5. *Fibrinogen.*—This remains as the fifth factor in the system. It may be estimated very readily by the heat coagulation method outlined by Whipple and Hurwitz.[14] By a slight modification of this method Whipple[15] has demonstrated an increase in fibrinogen in two cases of lobar pneumonia and in one of acute hemorrhagic colitis, a great decrease in chloroform poisoning, experimental and clinical, a decrease in two cases of cirrhosis of the liver and in five cases of cachexia from varying causes. The same observer reports normal fibrinogen in eclampsia, aplastic anemia and cancer of the liver.

During the past winter we have used the methods outlined above in the following cases:

| | |
|---|---|
| Purpura | 5 |
| Spontaneous thrombosis | 1 |
| Cirrhosis of the liver | 4 |
| Chronic lymphatic leukemia | 1 |
| Secondary anemia and sarcoma | 1 |
| Pernicious anemia | 7 |
| Total | 19 |

Our results in the non-anemic cases may be summarized as follows:

1. Purpura: Platelet count was reduced in two cases. Other factors were normal.

2. Spontaneous Thrombosis: Platelets were not studied. Other factors were normal.

3. Cirrhosis of the Liver: Platelets were not studied. Fibrinogen was low in one advanced case with bleeding from the gums and purpura. Other factors were normal in the other cases.

4. Chronic Lymphatic Leukemia: Platelets were not studied. Other factors were normal.

We shall report one case of pernicious anemia in full, since it seems to illustrate the bleeding type of this disease, and we shall mention other cases as they control these observations.

13. Addis, T.: The Pathogenesis of Hereditary Haemophilia, Jour. Path. and Bacteriol., 1911, xv, 427.

14. Whipple, G. H., and Hurwitz, S. H.: Fibrinogen of the Blood as Influenced by the Liver Necrosis of Chloroform Poisoning, Jour. Exper. Med., 1911, xiii, 136.

15. Whipple, G. H. Fibrinogen: 1. An Investigation Concerning its Origin and Destruction in the Body, Am. Jour. Physiol., 1914, xxxiii, 50.

CASE REPORT

*History.*—P. L. C., aged 26, salesman, unmarried, was admitted June 3, 1914. Complaint, "Washed-out looking — weakness." Family history and habits are entirely negative. There is no history of bleeding in the family.

*Previous Medical History.*—Measles and diphtheria in childhood. No history of whooping-cough, scarlet fever, typhoid, pneumonia, pleurisy, nor malaria. Cardiorespiratory: no history of dyspnea, nor edema of the feet nor ankles. He has never been subject to colds, tonsillitis, chronic cough nor night sweats. Gastro-intestinal: digestion always has been good. "Can eat anything." He has never had periods of vomiting nor epigastric distress. Genito-urinary: he has had no polyuria, dysuria nor nocturia. Nervous: there is no history of paralysis, injury nor operation; of areas of anesthesia nor paresthesia. No headache nor vertigo were present prior to the present illness. For the past three years he has noticed that the sight of his left eye has been somewhat diminished and indistinct.

*Present Illness.*—In August, 1913, the patient's friends called his attention to his loss of color. From this time until March, 1914, the patient kept at his work and took iron with fair steadiness, but became constantly paler and more yellow. About May 10 severe occipital and frontal headaches developed. These lasted all day and were accompanied by periods of vertigo, especially noticeable when the patient suddenly sat upright. At the same time there was marked weakness in the muscles, with dyspnea and frequent attacks of sharp cramps in the legs when walking. Three days ago the headaches became less severe, but his appetite disappeared completely. There were no nausea, vomiting, gastric pain, nor discomfort with this. Two weeks ago he noticed dark colored stools on one occasion. There has been no history of large gastric nor intestinal hemorrhage. For several weeks there has been a marked tendency to bleed from the gums. The patient has been compelled to stop brushing his teeth as this starts bleeding which will last several hours.

Of late there has been increased dimness of vision in both eyes. His best weight was 138 pounds one year ago; present weight 124 pounds.

*Physical Examination.*—The patient subjectively is entirely comfortable. Skin is very pale, yellow, moist and smooth.

Eyes: Pupils are equal, round, regular and react promptly to light and distance. There is no nystagmus or strabismus. Eye-grounds: O. D., disc is pale, vessels over it are poorly made out. Entire remaining area of fundus is covered with radiating hemorrhage. O. S. disc is outlined with fair sharpness. Hemorrhagic condition similar to that of O. D. is present.

Ears and Nose: Normal.

Mouth: Mucous membranes are very pale. Teeth are in good condition. At the junction of teeth and gums there are a few small blood clots. Tongue is protruded in mid-line without tremor. Tonsils are not enlarged.

Neck: Normal.

Chest: Lungs are clear, resonant and normal throughout.

Heart: There is no enlargement. There is a soft systolic murmur obscuring the first sound. This is well heard at the apex but is not transmitted to the axilla. At the base a rough, blowing systolic murmur is present, best heard in the third left interspace. Pulmonic second is greater than aortic second.

Pulses: Are regular, rapid, equal, synchronous and collapsing. Rate 128. Marked pistol shot sound is heard in the groin. Blood-pressure: systolic, 145; diastolic, 70.

Abdomen: No masses, tenderness, nor rigidity made out. Slight distention is present.

Liver is not enlarged.

Spleen is not enlarged.

TABLE 1.—Factors of Coagulation and Blood Examinations

| Date | Coagulation Time | Prothrombin | | Antithrombin | | Fibrinogen, Gm. | Platelets | Hemoglobin, Per Cent. | R.B.C. | W. B. C | Polynuclears, Per Cent. | Large Round, Per Cent. | Lymphocytes, Per Cent. | Eosinophils, Per Cent. | Nucleated cells Per Cent. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | P. L. C. | Control | P. L. C. | Control | | | | | | | | | | |
| June 4..... | ..... | ..... | ..... | ..... | ..... | ..... | 2,800 | 29 | 752,000 | 3,200 | 54 | 4 | 41 | 1 | 0 |
| June 5..... | 27 min. | 2-19 min.<br>3-25 min.<br>4-25 min.<br>5-72 min. | 11 min.<br>10 min.<br>10 min.<br>12 min. | 4-7 hrs.<br>5-34 min.<br>6-18 min. | 7 hrs.<br>37 min.<br>27 min. | 0.4204 | | | | | | | | | |
| June 11..... | 21 min. | 2-19 min.<br>3-17 min.<br>4-18 min. | 6 min.<br>6 min.<br>4 min. | 4-12 hrs.<br>5-26 min.<br>6-18 min. | 12 hrs.<br>12 hrs.<br>26 min. | 0.375 | 40,000 | 24 | 512,000 | 3,600 | 60 | 15 | 25 | 0 | 2 |
| Before transfusion | | | | | | | | | | | | | | | |
| After transfusion | ..... | 5-18 min. | 7 min. | ..... | ..... | ..... | ..... | 39 | 1,360,000 | 6,800 | | | | | |
| June 12..... | 25 min. | 2-9 min.<br>3-8½ min<br>4-9½ min.<br>5-15 min. | 4 min.<br>3½ min.<br>3½ min.<br>4 min | 4-0 min.<br>5-12 hrs.<br>6-30 min. | 0 min.<br>60 min.<br>7 min. | 0.500 | 112,000 | 44 | 1,100,000 | 3,200 | 66 | 2 | 32 | 0 | 1 |
| June 16..... | ..... | ..... | ..... | ..... | ..... | ..... | 3,200 | 34 | 920,000 | 2,800 | 48 | 16 | 36 | 0 | 1 |
| June 17*..... | 45 min. | 2-33 min.<br>3-24 min.<br>4-29 min.<br>5-33 min. | †<br>8 min.<br>6½ min.<br>6½ min. | 4-28 min.<br>5-17 min.<br>6-17 min. | 28 min.<br>16 min.<br>16 min. | 0.453 | ..... | .. | 1,040,000 | 2,000 | | | | | |
| Before transfusion | | | | | | | | | | | | | | | |
| June 18..... | ..... | ..... | ..... | ..... | ..... | ..... | ..... | 46 | 2,100,000 | 3,300 | | | | | |
| June 20..... | ..... | 2-21 min.<br>3-18 min.<br>4-18 min. | 22 min.<br>16 min.<br>20 min.<br>22 min. | 4-7 hrs.<br>5-21 min.<br>6-10 min. | 7 hrs.<br>10 min.<br>5 min. | 0.400 | | | | | | | | | |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| June 24..... | ..... | ..... | ..... | ..... | ..... | ..... | 21,000 | 43 | 2,020,000 | ..... | 38 | 21 | 38 | 3 | 0 |
| June 25..... | ..... | ..... | ..... | ..... | ..... | ..... | ..... | 58 | 2,840,000 | 2,600 | 56 | 10 | 33 | 1 | 0 |
| Transfusion June 24 | | | | | | | | | | | | | | | |
| June 30..... | ..... | ..... | ..... | ..... | ..... | ..... | 6,600 | 43 | 1,046,000 | 2,600 | 51 | 13 | 35 | 1 | 0 |
| July 1..... | ..... | ..... | ..... | ..... | ..... | ..... | 12,000 | 49 | 2,000,000 | 2,200 | 56 | 14 | 30 | 0 | 2 |
| Transfusion June 30 | | | | | | | | | | | | | | | |
| July 7..... | 22 min. | 2-19 min. | 15 min. | 4-20 min. | 17 min. | 0.420 | 25,000 | 36 | 1,140,000 | 2,900 | 44 | 14 | 40 | 2 | 0 |
| Before transfusion | | 3-42 min. | 14 min. | 5-6 min. | 17 min. | | | | | | | | | | |
| | | 4-27½ min. | 10½ min. | 6-6 min. | 5 min. | | | | | | | | | | |
| | | 5-42 min. | 17 min. | | | | | | | | | | | | |
| After transfusion | ..... | ..... | ..... | ..... | ..... | ..... | 23,000 | 45 | 1,710,000 | 2,800 | 40 | 22 | 36 | 2 | 0 |
| July 14..... | 18 min. | 2-45 min. | 9 min. | 4-20 min. | 45 min. | 0.350 | ..... | 46 | 1,940,000 | 3,000 | 58 | 10 | 30 | 2 | 0 |
| | | 3-16 min. | 8 min. | 5-45 min. | 11 min. | | | | | | | | | | |
| | | 4-16 min. | 8 min. | 6-45 min. | 11 min. | | | | | | | | | | |
| | | 5-90 min. | 7 min. | | | | | | | | | | | | |
| July 20..... | ..... | ..... | ..... | ..... | ..... | ..... | 48,000 | 38 | 1,400,000 | 3,400 | 62 | 8 | 27 | 3 | 0 |
| July 21..... | ..... | ..... | ..... | ..... | ..... | ..... | 62,000 | 60 | 2,060,000 | 3,000 | 65 | 5 | 26 | 4 | 0 |
| After transfusion | | | | | | | | | | | | | | | |
| July 27..... | ..... | ..... | ..... | ..... | ..... | ..... | ..... | 50 | 2,000,000 | 5,000 | 49 | 3 | 37 | 1 | 1 |
| July 29..... | ..... | ..... | ..... | ..... | ..... | ..... | ..... | 57 | 2,600,000 | 2,400 | 74 | 7 | 18 | 1 | 0 |
| After transfusion | | | | | | | | | | | | | | | |
| August 11.... | 18 min. | 2-18½ min. | 4½ min. | 4-1½ hrs. | 1½ hrs. | 0.300 | 40,000 | 32 | 1,050,000 | 4,500 | | | | | |
| | | 3-22½ min. | 4 min. | 5-1½ hrs. | 1½ hrs. | | | | | | | | | | |
| | | 4-23½ min. | 4 min. | 6-10 hrs. | 1½ hrs. | | | | | | | | | | |
| | | 5-29 min. | 3½ min. | | | | | | | | | | | | |

* On and after this date antithrombin plasma diluted 1:1 with 0.9 per cent. NaCl.
† Lost.

Extremities: There are no edema, scars, cyanosis, or sclerosis of peripheral vessels. Color of the skin everywhere is very light yellow.

Reflexes: Knee, ankle, biceps, triceps, supinator, and pronator reflexes are easily obtained and very active. There is a marked patellar clonus. No ankle clonus, Gordon sign, Oppenheim sign, nor Babinski sign made out.

On admission the temperature was 99.2 F. Pulse, 128. Respiratory rate, 21.

BLOOD EXAMINATIONS AND CLINICAL NOTES

June 4. Blood:

| | |
|---|---|
| Hemoglobin | 29 per cent. |
| R. B. C. | 752,000 |
| W. B. C. | 3,200 |
| Platelets (23) | 2,800 |

Differential Count: Polymorphonuclear neutrophils, 54 per cent; large mononuclear cells, 4 per cent.; lymphocytes, 41 per cent.; eosinophils, 1 per cent. Red cells show very slight anisocytosis and poikilocytosis, no polychromatophilia, stippling, or basophilia. No myelocytes, normoblasts, or megaloblasts are seen.

The puncture wound from which blood was taken for counting bled for forty-five minutes and was finally checked with nitrate of silver. This prolonged bleeding time was constant and necessitated subsequently the use of a very fine needle. Warned by this experience, the venous punctures recorded later were made with a fine needle and no trouble occurred.

Urine: Negative.

Wassermann reaction blood serum, negative.

The patient was at once placed on ascending doses of Fowler's solution, dilute hydrochloric acid with meals, and forced house diet. He was kept at rest in bed out of doors all of the time.

June 5, blood obtained by venous puncture.

Coagulation time, twenty-seven minutes. (Howell's method.)

TABLE 2.—CASE P. L. C. DETERMINATION OF ANTITHROMBIN

| Thrombin, Drops | Heated Plasma, Drops | Fibrinogen, Drops | Result |
|---|---|---|---|
| 4 | 1 | 10 | Clot in 7 hours. |
| 5 | 1 | 10 | Clot in 34 minutes. |
| 6 | 1 | 10 | Clot in 18 minutes. |
| | CONTROL C. K. D. | | |
| 4 | 1 | 10 | Faint clot in 27 minutes; firm clot in 7 hours. |
| 5 | 1 | 10 | Clot in 37 minutes. |
| 6 | 1 | 10 | Clot in 18 minutes. |

PROTOCOLS

The following protocols illustrate the methods used for determining antithrombin and prothrombin. For further studies of these factors and for their correlation with the changing blood picture, reference must be made to Table 1.

Antithrombin was determined by Howell's method. The test plasma is heated slowly to 60 C. and then centrifugalized to throw down the fibrinogen which has been precipitated. If a drop of the supernatant fluid is added to a known thrombin solution it can be shown to delay the action of this thrombin on fibrinogen most markedly. In every test the supposedly abnormal plasma

must be compared with plasma from a normal individual, the two being treated in the same way, their comparison indicating the abnormality, if it exists.

The patient's antithrombin was entirely comparable to that of the control and in this factor no abnormality existed. For tests made on June 17 and following dates heated plasmas were diluted 1:1 with 0.9 per cent. NaCl in order to shorten the time necessary for the experiment.

Prothrombin was determined by recalcifying oxalated plasma. Ability to invert a 10 mm. tube without dislodging the clot has been taken as the end-point throughout our entire series of observations on prothrombin. In these tests, as with antithrombin, comparison with normal plasma is necessary. Prior to July 7 the test bloods and the controls were centrifugalized simultaneously to obtain the plasma, but the duration of centrifugalization varied on different occasions. On and after this date the same speed and same time were used.

TABLE 3.—CASE P. L. C. DETERMINATION OF PROTHROMBIN

| Oxalated Plasma, Drops | 0.5 Per Cent. $CaCl_2$, Drops | Result |
|---|---|---|
| 5 | 2 | Invertible in 19 minutes. |
| 5 | 3 | Invertible in 25 minutes. |
| 5 | 4 | Invertible in 25 minutes. |
| 5 | 5 | Invertible in 72 minutes. |
| | CONTROL C. K. D. | |
| 5 | 2 | Invertible in 11 minutes. |
| 5 | 3 | Invertible in 10 minutes. |
| 5 | 4 | Invertible in 10 minutes. |
| 5 | 5 | Invertible in 12 minutes. |

The patient's plasma coagulated more slowly than the control, indicating a prothrombin deficiency.

Fibrinogen was determined by the heat coagulation method: 10 c.c. of oxalated plasma are heated to 60 C. and kept at this temperature for twenty minutes. The resultant coagulum is filtered off, washed and weighed. This process is adequate for showing gross alterations in fibrinogen but very inaccurate for small variations.

*Fibrinogen.*—0.4204 gm. in 100 c.c. oxalated plasma.

June 10: For the past two days the patient has been spitting blood constantly and this evening vomited 500 c.c. of dark bloody material. He refuses nourishment and appears to be failing fast.

June 11: Condition is unimproved. Transfusion was decided on and 750 c.c. of whole blood were introduced by the indirect method from the patient's father. During exposure of the patient's veins there was a large amount of troublesome oozing. This occurred in subsequent transfusions, but always decreased as the new blood was given. About one-half hour after transfusion a few purpuric spots appeared on the patient's forearms. Bleeding from the gums stopped promptly and there was no subsequent hemoglobinuria nor elevation in temperature.

June 12: Transfusion has resulted in an increased platelet count and increased prothrombin. Fibrinogen has risen slightly but not enough to be significant.

June 14: Bleeding from the gums has recommenced.

June 16: Oozing from gums continues. Pulse rate has risen. The rapidly falling red count is an indication for a second transfusion.

TABLE 4.—Anemic Cases with Slightly Decreased Prothrombin

| Case | Prothrombin | | Hemoglobin, Per Cent. | R. B. C. | W. B. C. | Polynuclears, Per Cent. | Large Round, Per Cent. | Lymphocytes, Per Cent. | Eosinophils, Per Cent. | Nucleated Cells |
|---|---|---|---|---|---|---|---|---|---|---|
| | Case, Min. | Control Min. | | | | | | | | |
| VI | 2- 9 | 9 | 67 | 2,400,000 | 5,400 | 54 | 5 | 38 | 3 | 0 |
| | 3- 9¼ | 6 | | | | | | | | |
| | 4-10 | 8 | | | | | | | | |
| | 5-13 | 8½ | | | | | | | | |
| III | 2-11½ | 9 | 43 | 1,080,000 | 4,600 | 70.5 | 5 | 23 | 1 | 0 |
| | 3-12 | 9 | | | | | | | | |
| | 4-12 | 9 | | | | | | | | |
| | 5- 9½ | 9 | | | | | | | | |
| IV | 2- 9 | 6 | 60 | 1,724,000 | 6,400 | 83 | 3 | 10 | 4 | 6 |
| | 3- 9 | 5 | | | | | | | | |
| | 4- 9 | 5 | | | | | | | | |
| | 5-12 | 5 | | | | | | | | |
| V | 2- 0 | 6 | 21 | 620,000 | 3,000 | 68 | 3 | 29 | 0 | 0 |
| | 3- 9½ | 5 | | | | | | | | |
| | 4- 9½ | 5 | | | | | | | | |
| | 5-11½ | 5 | | | | | | | | |

June 17: 750 c.c. of blood were given. There was immediate cessation of bleeding and immediate improvement.

June 20: Gums are not bleeding and the patient is in fine spirits, with excellent appetite. Prothrombin observed on this day parallels the control.

June 24: Gums bled severely all last night and are bleeding this morning. Pulse is weak. 750 c.c. of blood by indirect transfusion from father caused immediate cessation of bleeding and general improvement.

June 30: A great deal of bleeding from the gums recurred yesterday and last evening. During the night 50 c.c. of defibrinated human blood were injected intramuscularly. To-day the bleeding is not so rapid nor profuse and clots tend to form on the bleeding surfaces. Transfusion was again done, 650 c.c. being given. Hemorrhage stopped at once and a comfortable night's sleep ensued.

July 4: Patient has developed a sore throat with peritonsillar swelling on the right side. Gums bled constantly all afternoon and he vomited his supper with a quantity of swallowed blood.

White blood cells, 2,400. No increase of leukocytes was noted with this infection, which however, was severe enough to send the temperature to 102 F.

July 5: Gums are bleeding more severely; 11 c.c. human blood serum were given intramuscularly.

July 6: Fowler's solution was omitted; 10 c.c. human blood serum were given intramuscularly. This injection was followed by slight abatement of

bleeding during seven or eight hours, but then it started again and became very severe; 0.2 gm. salvarsan was given intramuscularly.

July 7: Excessive bleeding from the gums was present this morning and after a very restless night. Defibrinated human blood, 44 c.c., were given in the morning but the bleeding was not affected in the least; 750 c.c. of blood were given by transfusion during the afternoon and bleeding ceased immediately.

July 14: Slight oozing is present this morning between the two upper right pre-molars.

July 16: Salvarsan, 0.2 gm., was given intravenously.

After this date the patient's course continued much the same. On July 21 he received 750 c.c. of blood and on July 29, 900 c.c. and 0.2 gm. of salvarsan intravenously. These transfusions like the others were necessitated by a rapidly falling blood count due to bleeding from the gums and to failure of regeneration. Thorough removal of tartar collections from the teeth remedied somewhat the bleeding tendency but did not prove of permanent value. August 10 splenectomy was proposed and refused. Following refusal of operation the patient left the hospital for his home. He was seen one week later and was evidently failing fast. In ten more days he died and no autopsy could be obtained.

## DISCUSSION OF CASE AND CONCLUSIONS

If we consider the entire course of this anemia it seems to have been distinguished chiefly by failure to regenerate blood-cells and by a tendency to bleed. In a recent analysis of aplastic pernicious anemia, Musser[16] emphasizes certain essential characteristics of this disease. These are:

1. Young males are most frequently affected.

2. Remissions do not occur.

3. Subcutaneous hemorrhages and hemorrhage from mucous membranes are extremely frequent. In four of the fifty-nine reported cases sudden hemorrhage was the first manifestation of the disorder.

4. Fever is a constant symptom and often reaches a high point in the disease. In our case fever was constant, but 102 F. was the highest point reached.

5. A low color index is the rule. This was not observed by us, the color index being constantly above 1.

6. Leukopenia is constantly present and is caused by absence of granular forms. Leukocyte counts rarely exceed 2,000 and polymorphonuclear forms constitute from 8 to 20 per cent., instead of the usual 70 per cent. There is relative lymphocytic increase.

We noted constant decrease of polymorphonuclear cells with increased lymphocytes, but our percentages have never been so marked as those mentioned by Musser.

16. Musser, J. H.: Study of a Case of Aplastic Anemia, THE ARCHIVES INT. MED., 1914, xiv, 275.

7. Nucleated red forms, polychromatophilia, stippling and poikilocytosis are absent. Anisocytosis is found occasionally, with a tendency to macrocytosis. In twenty-five differential counts we found nucleated red cells ten times, three being the highest number seen. Other characteristics of the red cells corresponded very well with the ruling observations in these anemias.

It seems safe to regard the case as one of fairly complete aplasia. We have not found any extensive studies of the factors of coagulation in bleeding anemias. Musser records a prolonged coagulation and bleeding time in his case, and also notes the fact that 20 c.c. of horse serum with 1 gm. doses of calcium lactate four times a day did not check the tendency. Whipple[5] reports a case of undoubted aplastic anemia in which there was epistaxis and constant uncontrollable oozing from the gums. This patient was given 500 c.c. of defibrinated blood by indirect transfusion, with no effect on the hemorrhagic process. Bleeding time was prolonged, but coagulation time appeared normal. Blood was taken from the heart one hour and twenty-five minutes after death and an increase in antithrombin found. Prothrombin was normal and fibrinogen undetermined. The prothrombin and antithrombin studies used in this case were not subjected to the controls which Howell's later paper emphasized as necessary.

In our case we have noted the following facts:

1. Coagulation time was distinctly prolonged once only (July 17); bleeding time was always long.

2. Platelets were always far below normal and were not consistently increased by transfusion.

3. Antithrombin was consistently normal and was not altered by transfusion.

4. Fibrinogen was normal throughout and was unaffected by transfusion.

5. Prothrombin was constantly decreased, but was subject to transient slight increase by transfusion.

We have felt that throughout the entire clinical course of this patient the prothrombin reaction has given us an excellent indication of the effective clotting power of the plasma. The end-point used in the test expresses complete solid coagulation. Clotting may begin in normal time, but the process, instead of requiring a few minutes as in ordinary plasmas, takes many minutes. We have been interested to note that the plasma from other cases of pernicious anemia, essentially formative in character, shows the same tendency, but to a very slight degree. In none of these, however, has there been a history of hemorrhage and all have been regenerative and have passed into periods

of remission. Table 4 presents four such cases. Unfortunately, these observations are not accompanied by platelet counts, the importance of this factor being unappreciated when they were made. Fibrinogen and antithrombin were normal and the blood picture indicates the severity of the anemia.

Our studies seem to emphasize the following points:

1. Prothrombin is diminished slightly in all cases of pernicious anemia.

2. This diminution is not great and is unimportant if active regeneration is in progress.

3. Antithrombin and fibrinogen are normal even in the presence of very low cell counts.

4. In one case in which there has been pronounced diminution in prothrombin, platelet counts have been strikingly low, and the picture throughout has been that of fairly complete aplasia.

We wish to express our thanks to Dr. K. R. Drinker for many fibrinogen determinations throughout this work.

# THE ORIGIN OF THE PROTEINS OF NEPHRITIC URINE*

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From time to time attempts have been made to determine the source of the protein present in albuminous urine. Chemical methods are, in most forms of albuminuria, entirely incapable of distinguishing between blood proteins, kidney proteins and urinary proteins. The most definite exception to this statement is furnished by the peculiar protein of "myelopathic albumosuria," which is distinctly different from any protein found in normal blood or tissues. With the advent of the precipitin reaction came the possibility of distinguishing sharply between proteins from different species of animals, which made it feasible to investigate the urinary proteins in relation to their original source, i. e., to determine whether they come unchanged from the food proteins, or have the character of human proteins. Several studies of this kind have been reported, but not with constant results. So discordant and widely scattered is the literature on this topic that it has seemed advisable to collect and analyze the evidence at some length.

All are agreed that foreign proteins introduced parenterally are at least in part quickly excreted by the kidneys in unchanged form, which establishes the fact that the kidney *can* excrete proteins coming to it from the blood, whatever bearing this fact may have on the question as to whether urinary proteins in nephritis come directly from the blood or not.

Ascoli[1] found by means of the precipitin test that, after eating eggs, the urine of healthy men and of nephritics gives reactions for both egg and serum proteins. In some individuals, however, he was able to demonstrate the presence of egg albumin in the blood and not in the urine, showing that there may be a certain amount of foreign protein absorbed unchanged and yet not eliminated in the urine in demonstrable quantities. He found that after eating beef or chicken the corresponding proteins may be demonstrable in the urine, in case they cause albuminuria.[2] Inouye[3] also found that precipitin reactions are given with anti-egg serums by the urine of some patients after eating excessive amounts of raw egg, but not by all. It would seem that infants are more likely to absorb proteins unchanged than adults, and Lust[4] found that, especially in diseased conditions of the alimentary canal in infants, egg-white may be detected in the urine by both precipitin and anaphylaxis

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* From the Department of Pathology, University of Chicago.

1. Ascoli: München. med. Wchnschr., 1902, xxvi, 734.

2. Ascoli: München. med. Wchnschr., 1903, l, 201 and 1761; Ztschr. f. physiol. Chem., 1903, xxix, 283.

3. Inouye: Deutsch. Arch. f. klin. Med., 1903, lxxv, 378.

4. Lust: Jahrb. f. Kinderh., 1913, lxxvii.

reactions. Bovine protein is much less readily demonstrated in the urine after feeding.

On the other hand, using the extremely delicate anaphylaxis test, which can detect much smaller quantities of the protein than the precipitin test, one of us was unable to demonstrate the presence of egg proteins in the urine of healthy men after eating large quantities of raw egg-white, whether albuminuria was produced or not.[5] If there was albuminuria the reactions were only for human proteins and not for egg proteins. But Minet and Leclercq[6] found that the urine of both normal and nephritic patients who have been given egg-white and milk may sensitize guinea-pigs to these same proteins; ordinary nephritic urine, they state, sensitizes only to human serum. Unfortunately their work is published only as a brief note, which does not permit of critical consideration.

Hecker[7] examined the urine of six infants, fourteen children, and three adults and obtained precipitin reactions with antibovine serum with the urine of one infant and five children. In five of these six cases the urine also reacted with antihuman serum, and in one for a time only the bovine reaction was obtained. This result, however, is not duplicated by Krasnogorski,[8] who examined by both the precipitin and the complement fixation reactions the urine from twenty children, and in no case could he demonstrate the presence of the proteins which were being received in the food.

Whether the urinary protein in nephritis comes from the blood through damage to the capillary walls, as is commonly assumed, or is derived from the renal epithelium, is not a new question, but renewed interest is given to it by the suggestive studies and theories of nephritis and edema of Martin H. Fischer. According to him the urinary protein is derived from the renal cells which have been dissolved under the influence of acids. We do not understand Fischer to contend that this is the sole source of the urinary protein, but it is evident from the general considerations in his book that he looks on this as the most important source. Since our biologic methods have been refined so that, at least under certain conditions, different proteins from the same animal may be distinguished, it would seem feasible to investigate by these methods the source of the urinary proteins in albuminuria, and to determine whether the urinary protein is a blood protein, or is derived from the renal tissue, or is a mixture of the two, or, possibly, is entirely distinct from either.

The principle involved is that of saturation or exhaustion of common antibodies in immune serum, so that the specific antibodies which are left can then be detected. Thus, if an animal is immunized to a mixture containing protein *A* and protein *B*, its serum will react with either protein. After saturating all the antibodies for *A*, by permitting reactions to occur with enough of *A* to combine them all, the antiserum should still contain antibodies for *B*, which can then be demon-

5. Wells, H. G.: Jour. Am. Med. Assn., 1909, lxiii, 863.
6. Minet and Leclercq: Compt. rend. Soc. de biol., 1912, lxxiii, 464.
7. Hecker: München. med. Wchnschr., 1909, lvi, 1875.
8. Krasnogorski: Ztschr. f. Kinderh., 1912, iv, 526.

strated. For example, it is practically impossible to prepare an extract of kidney or other organ which will not contain more or less blood proteins, no matter how carefully we may wash out the organ before extracting the proteins, hence, if we immunize a rabbit with such an extract, its serum will presumably contain antibodies for kidney proteins and also for blood proteins.[9] To demonstrate that the human kidney does contain antigenic proteins distinct from those of the blood of the same animal we may take such an antikidney serum, permit it to react with human blood-serum until it will no longer give a precipitate with fresh quantities of blood-serum, and then test it with kidney extract; the production now of a precipitate with the kidney extract is presumptive evidence that this extract contains some antigen which is not present in the blood-serum of the same animal.

By using this saturation method, Grund[10] demonstrated readily that human liver, kidney and spleen contain specific organ antigens. That is, antiserums for these several organs, when saturated with the homologous serum, would still give a precipitin reaction with the specific organ extract; or, conversely, antiserum for human blood when saturated with the organ extracts was still reactive with blood-serum. It was much more difficult to secure evidence of specificity between the different organs, especially between liver and kidney, although the differentiation of these organs from muscle was well defined. Numerous other more recent studies have shown much the same result, namely, that there are organ-specific proteins which can be differentiated by the precipitin reaction through the saturation method, but that this is not easy to do. Apparently in general the serum is more easily differentiated from the organ proteins than are the latter from each other.

This same principle of saturation can be utilized with the anaphylaxis reaction, as has been shown in a series of experiments with the proteins of the hen's egg and with certain vegetable proteins by Wells, and Wells and Osborne,[11] a fact which strongly supports the hypothesis that the refractory or desensitized state of guinea-pigs recovered from anaphylactic reactions depends on an exhaustion of the specific antibodies that are responsible for the anaphylactic state. Here the procedure is to inject the sensitized guinea-pig with one of the antigenic proteins until it no longer reacts, and then, after an interval of twenty-four to forty-eight hours, inject the other antigenic protein. A reaction with this second protein indicates that it or a corresponding antigen

9. See, for example, Minet and Bruyant, Compt. rend. Soc. de biol., 1911, lxxi, 166.

10. Grund: Deutsch. Arch. f. klin. Med., 1906, lxxxvii, 148.

11. Wells and Osborne: Jour. Infect. Dis., 1911, ix, 147; 1913, xii, 341.

was present in the material used for sensitizing, as well as the antigen which sensitized to the first protein to which the animal has been made refractory.

We can find in the literature little evidence bearing on the possibility of a renal origin for the protein of nephritic urine, as tested by the biologic methods. Grund,[10] in the paper previously referred to, reports the following experiments: Antirenal serum was saturated with blood serum and thus made specific for renal proteins, and was then found to give *no* precipitin reaction with urine protein from ten different cases, even when it had given a good reaction with the same urine before being saturated with serum. Anti-serum for human serum proteins, which had been saturated with renal extract, did give reactions with the urine from four cases of nephritis. These results indicate that urinary proteins, at least in nephritis, come from the blood and do not exhibit the biologic characteristics of specific renal proteins. As Grund states, however, the possibility that small quantities of renal protein may be present in the urine is not excluded by these experiments, but, if present at all, it presumably is in very small amounts.

Later, a more extensive paper was published as an inaugural dissertation by Eva Moritz.[12] She found that urinary protein gives a precipitin reaction with antiserum from a rabbit immunized with urinary protein, even after saturation of the antiserum with human serum; likewise urinary protein saturated with antiserum for human blood is still reactive for antiserum for urine proteins. These experiments indicate that urinary protein is different from blood protein, which is quite the opposite from the finding of Grund. With antikidney serums the results were more ambiguous, but they generally gave reactions indicating that blood proteins and urinary proteins are not identical, but they did not show conclusively a difference between renal proteins and urinary proteins. Thus, two antirenal serums which reacted with both renal extract and urine protein, did not react with blood serum; also, antiurine serum when saturated with human serum still reacted with both urinary and renal proteins. Other antirenal serums were obtained, however, reacting with human serum and kidney extract, but not with urinary protein. Hence the conclusion is drawn by this investigator that urinary protein is not identical with either blood protein or the specific renal protein, and that if renal constituents are present in nephritic urine they must be extremely small in quantity. Urinary protein is, according to these deductions, a specific protein of itself, different from either blood or kidney cell proteins.

More recently Doerr and Pick[13] have reported experiments on the antigenic properties of urine proteins, and in their discussion they refer to certain other workers in the field, but unfortunately without quoting references whereby the original articles could be consulted. Among their citations is an article by Landsteiner and v. Eisler, who obtained precipitins by immunizing with normal human urine, which reacted with urine and with extract of human kidney; but they found that antisera produced by immunizing with human blood caused little or no reaction with normal human urine, and hence concluded that the antigen of normal urine must be different from the antigen of serum and perhaps derived from the kidney itself. The antiserums obtained by these authors by immunizing with urine were not very strong, and some subsequent observers have doubted that the reactions observed were true precipitin reactions. Doerr and Pick, however, also found that the serum of a rabbit immunized with normal human urine (giving no chemical reactions for protein) gave precipitin reactions with extracts of human kidney, but not

12. Moritz, Eva: Beiträge zur serologischen Untersuchung der Harneiweisses, Freiburg i. Br., Speyer and Kaerner, 1911.

13. Doerr and Pick: Ztschr. f. Immunitätsf., 1914, xxi, 463.

with extracts from other organs or human serum. The antigen of normal urine also shows a characteristic seen with renal extracts, in that antiserum for horse urine contains amboceptors that are lytic for sheep erythrocytes and toxic for normal guinea-pigs. Furthermore, the amount of protein present in nephritic urine has no relation to the amount of this peculiar heterogenetic antigen found in normal urines, which is characterized by not being specific for the species from which it originates. Hence Doerr and Pick seem to have demonstrated that in normal urine there is an antigen which probably is derived from the renal cells and not from the blood, but which probably is not the same as the protein excreted in nephritis. Their experiments do not establish the source of the latter.[14]

While we were engaged in the present investigation, G. Salus[15] published a study of the antigenic properties of "organ plasma" prepared by Pohl's method, and found that such organ plasma, if free from blood, is entirely distinct from the antigens of blood. That is, in his experiments, antibodies (precipitins, anaphylactins, and complement-binding) for serum did not give reactions with organ plasma, or conversely. He then took up specifically the question of the origin of the protein in nephritic urine on the basis of this observation, and summarizes his results as follows: Antiserum for human serum gives precipitin reactions with nephritic urine but not with kidney protein, and antiserum for nephritic urine reacts with human serum; hence the urine must contain the same antigens as the serum. Antiserum for human kidney contained neither precipitins nor complement-binding antibodies for either human serum or nephritic urine; hence the latter does not contain the antigens characteristic of kidney tissue. Guinea-pigs sensitized with nephritic urine or blood serum did not give anaphylaxis reactions with kidney plasma, and animals sensitized with this plasma were reactive to serum or urine only when the plasma gave distinct reactions for blood. He therefore concludes that the protein of nephritic urine must be serum protein, and not renal tissue protein.

Examining the protocols, however, we find that these conclusions are based on a small number of experiments. For example, the statement that human serum does not sensitize to human kidney plasma is based on *one* experiment; while the reverse reaction was tried but twice. As for the experiments between kidney plasma and urine, we find but six; of three guinea-pigs sensitized with human kidney, two gave no reactions with human nephritic urine, and one gave a slight reaction; of three sensitized to nephritic urine, one gave no reaction to human kidney, one gave a slight reaction and one died; the positive reactions are ascribed by Salus to admixed blood or pus. Surely no one familiar with the requirements of anaphylactic experiments would be willing to draw positive conclusions from such a meager and variable set of results as this, and the statement that has been made that these experiments settle Fischer's theory of nephritis is totally unwarranted.[16]

From this review of the literature it is apparent that the available evidence on the origin of the urinary protein, whether in alimentary albuminuria or in nephritis, is entirely contradictory, and therefore of little value in drawing any conclusions. Presumably, part of the contradictions depend on the difficulties inherent in the available methods

14. In another paper (Biochem. Ztschr., 1914, lx, 257) discussing the antigenic property of extract of horse kidney, they note that it is not anaphylactogenic for guinea-pigs, but do not state whether the antigen of horse urine exhibits the same characteristic.

15. Salus, G.: Biochem. Ztschr., 1914, lx, 1.

16. A controverted theory of nephritis, editorial, Jour. Am. Med. Assn., lxii, 1971.

for distinguishing, even by the biologic reactions, between different proteins coming from the same animal. There should be, it would seem, no difficulty in differentiating egg or milk proteins from human proteins, nevertheless there are remarkable contradictions in the reports concerning the presence of foreign proteins in the urine in alimentary albuminuria. This being so, the distinction of the closely related proteins of urine, kidney and serum of the same species, must be a task of exceeding difficulty. It is evident, therefore, that there is need for more work, and especially for more careful work, in this field, and we have endeavored to seek further evidence on the disputed points.

## AUTHORS' EXPERIMENTS

Our experiments were conducted as follows:

Urinary protein was obtained by collecting large amounts of urine from patients with chronic parenchymatous nephritis, preserving with chloroform, dialyzing against cold running water until but a small proportion of the crystalloids remained, and then rapidly drying at room temperature by exposing in thin layers to an air current. The product thus obtained was found on analysis to contain 39.4 per cent. of soluble coagulable protein in one preparation, and in another 58.5 per cent.

Kidney protein was obtained from fresh, practically normal human kidneys, by washing the chopped tissue to remove as much blood as possible, extracting with water in the cold, and preserving the watery extract with chloroform. This extract contained 2.5 per cent of soluble, heat-coagulable protein. It contained, of course, a considerable proportion of blood, but by use of the saturation method this difficulty should be overcome in biologic tests.

Guinea-pigs of about 250 to 300 grams were sensitized with the following amounts of each material:

Urinary protein, .005 gm.

Kidney protein, 0.5 c.c. extract, or 0.0125 gm. protein.

Human serum, 0.1 c.c.

After an interval of twenty to thirty days they were injected with the heterologous protein in the following amounts:

Urinary protein, 0.05 to 0.10 gm. crude material, or 0.020 to 0.058 gm. protein. Kidney protein, 2 to 5 c.c. of extract, or 0.05 to 0.125 gm. protein. Human serum, 0.1 c.c. to 0.6 c.c., after heating one hour at 56 C. to remove "primary toxicity."

A second dose of the same amount of heterologous protein was given twenty-four to seventy-two hours later, to insure saturation of all antibodies specific for the foreign proteins which the animal might have developed. This was followed forty-eight to seventy-two hours later by an injection, usually of the protein used for sensitizing, to ascertain if there had been developed antibodies specific for this protein and not reacting with the heterologous protein. Frequently the third of our proteins was injected later, to see if any antibodies for this protein were present.

Control experiments showed that our preparations were capable of producing severe, characteristic anaphylaxis reactions when the same protein was used for both sensitizing and intoxicating dose.

In view of the character of the results obtained, it scarcely seems necessary to give detailed protocols; hence the experiments are summarized in the accompanying table:

Abbreviations used in tables:

U—Urine protein.
S—Human serum.
K—Kidney protein.
A—Human ascites fluid.
0—No anaphylactic reaction.
+—Slight anaphylactic reaction.
++—Moderate anaphylactic reaction.
+++—Severe anaphylactic reaction.
±—Doubtful anaphylactic reaction.
d—Fatal anaphylactic reaction.

TABLE SHOWING REACTIONS IN ANIMALS SENSITIZED TO VARIOUS PROTEINS

SENSITIZED TO KIDNEY PROTEINS *

| | | | | |
|---|---|---|---|---|
| 1. | K d | — | — | — |
| 2. | K d | — | — | — |
| 3. | U ++ | U + | U 0 | S + |
| 4. | U ++ | U + | K + | S + |
| 5. | U ++ | U + | K + | S + |
| 6. | U ++ | U 0 | K 0 | S + |
| 7. | S ++ | S + | K + | U + |
| 8. | S ++ | S + | K + | U + |
| 9. | S ++ | S + | K 0 | U + |
| 10. | S ++ | S + | K 0 | U + |

* In all these experiments, unless otherwise specified, the interval after sensitization before injecting the first intoxicating dose was twenty to thirty days, and between each succeeding dose it was two days.

SENSITIZED TO SERUM PROTEINS

| | | | | |
|---|---|---|---|---|
| 1. | S d | — | — | — |
| 2. | S d | — | — | — |
| 3. | K ++ | K + | S + | U 0 |
| 4. | K ++ | K + | S + | U 0 |
| 5. | K ++ | K 0 | U 0 | — |
| 6. | U d | — | — | — |
| 7. | U d | — | — | — |
| 8. | U d | — | — | — |
| 9. | U ++ | U ± | S 0 | K 0 |
| 10. | U ++ | U ± | S 0 | K 0 |

SENSITIZED TO URINE PROTEINS

| | | | | |
|---|---|---|---|---|
| 1. | U +++ | — | — | — |
| 2. | U +++ | — | — | — |
| 3. | S ++ | S 0 | U 0 | K +† |
| 4. | S +++ | S 0 | U 0 | K + |
| 5. | S ++ | S 0 | U 0 | K + |
| 6. | S + | S 0 | U 0 | |
| 7. | K ++ | K 0 | S 0 | K + |
| 8. | K + | K 0 | S ± | K + |
| 9. | K ++ | K 0 | U 0 | K 0 |
| 10. | K +++ | K 0 | U 0 | K + |
| 11. | K ++ | K + | U 0 | |
| 12. | K ++ | K + | U 0 | |
| 13. | K ++ | K + | U 0 | |
| 14. | S +++ | S + | U 0 | K 0 |
| 15. | S +++ | S + | U 0 | K 0 |

† The injections recorded in this column were made seven days after the last preceding injection in Animals 3, 4, 5, 7, 8, 9 and 10, so that there had been time for a new sensitization to have resulted from the first intoxicating dose given eleven days before.

| | SENSITIZED TO ASCITES FLUID | |
|---|---|---|
| 1. U + | U 0 | A 0 |
| 2. U d | — | — |
| 3. U + | U 0 | A 0 |
| 4. U + | U 0 | A 0 |
| 5. U + + | U 0 | A 0 |
| 6. K + + | K 0 | A 0 |
| 7. K + + + | K 0 | A 0 |
| 8. K + + + | K 0 | — |
| 9. K + + | K 0 | A 0 |

Examining this table we find that the results are as uniform as can be expected in such a series of anaphylaxis experiments, permitting conclusions to be drawn with reasonable confidence. Without exception, guinea-pigs sensitized to any one of the three preparations — urinary proteins, renal extract and serum or ascites fluid, react strongly to either of the other two. This must mean that identical antigens are present in each. We also find that after saturation with the heterologous antigen the animals are refractory to the antigen used for sensitizing, which may be interpreted as indicating the absence in any one of the three proteins of any antigen not present in the other two which can be demonstrated by the method employed. That there may not be such specific antigens present in urine, serum and kidneys, as maintained by some previous observers, we do not pretend to deny on the basis of these experiments. Other methods may demonstrate them, but our experience with the saturation method in the detection of mixed antigens by anaphylaxis has indicated that this method usually is efficient.[17]

## CONCLUSIONS

The literature on the source of the proteins in the urine of nephritics contains such conflicting statements that it is impossible to decide whether urinary protein is derived from the blood or the kidneys, or is a specific protein distinct from the proteins of either blood or kidney. A series of experiments by the anaphylaxis method gave no evidence of the existence of antigens in either urine or kidney distinct from each other or from the antigens of human serum. This result does not answer the question of the origin of urinary protein, but merely indicates the inadequacy of the anaphylaxis method for the solution of the problem.

17. We also made attempts to develop precipitins and complement fixation antibodies by immunizing rabbits with these proteins, but without success.

# MERCURY NEPHRITIS *

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The instances of renal disease in which exclusively one portion of the anatomical structure of the kidney has received injury are so excessively infrequent that they at once excite interest as means of testing our conceptions of physiological functions of this organ and the mode of origin of some signs of disease. These conditions are, patently, those of successful experimentation. That the occasional cases of toxic nephritis in man have not been more fruitful in yielding information applicable to broader studies is due chiefly to the great rapidity and severity of the symptoms, culminating after a few days in death. Instances of fatal poisoning with mercuric chlorid are common, and there is a well recognized type of lesion found in the kidney in these cases; but as the period of life after ingestion of the poison is relatively brief, the signs and symptoms of renal injury are obscured and massed in those occasioned by a corrosive poison.

In the case of mercuric poisoning reported here the patient lived forty-one days, so that many of the features ordinarily seen in these cases, while present during the first week or more, were not sources of confusion at later periods in the disease.[1]

## CASE REPORT

*History.*—Mrs. A. R., aged 26, was brought to New York Hospital, May 26, 1914. She stated that she had that morning (8:30) taken six tablets for a headache. Shortly after, discovering that the tablets were mercuric chlorid, she sent for a physician. About half an hour after taking the tablets the patient vomited a large amount of material. On admission to the hospital at 10:15 a. m. the patient did not appear acutely ill. There were no excoriated areas in the mouth, though the pharynx was considerably congested. Other than some sensitiveness in the epigastrium the admission examination was negative. Lavage water containing gastric contents gave positive tests for mercury. A catheterized specimen of urine contained considerable albumin, numerous granular casts, but no blood. This specimen was not tested for mercury, but the metal was detected a number of times in the urine subsequently.

*Treatment and Course.*—Treatment was at once begun by frequent lavage of the stomach and bowel and an endeavor made to increase the fluids taken by the patient, supplemented by the Murphy drip. During the first day the

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1. The longest period of life recorded after swallowing poisonous amounts of mercuric chlorid is twenty-one days.

patient's mouth became sore, which interfered with the ingestion of anything. This symptom became worse and for two weeks there persisted an extreme degree of stomatitis and ptyalism which was an obstacle to the efforts made to spare the kidneys. The irritated condition of the gut was evidenced for ten days by frequent discharges, containing much mucus and blood. This state of affairs not only made the retention of the rectal tube painful, but seemed to decrease the absorption of water from the intestine.

There was fever up to 101 F. and a leukocytosis of 20,000 during the first week, after which both temperature and leukocyte counts were normal; the systolic blood-pressure varied between 100 and 140 mm. of mercury during the whole course of the sickness.

Due to the conditions mentioned the amount of water taken by mouth and absorbed from the intestine was not as large as desired; on May 30, 900 c.c. were retained and on June 4, the tenth day of the sickness, there were noted convulsive tremors involving all the muscles. Later there was a mild general convulsion and the patient was in a stuporous state the remainder of the day. This was repeated June 7, the thirteenth day of the illness, with more severity, although the urine volume had risen to 2,000 c.c. A state of semi-coma persisted for two days. As the patient became more conscious it was evident that there existed a mild toxic psychosis. On the whole, the general condition was regarded as good during the following two weeks. and a favorable prognosis was considered because of the improving state of renal activity. Vomiting had been a troublesome symptom from the start, but during the latter part of June this symptom came more into prominence, until scarcely anything was retained in the stomach. Any fluid or food was rejected. The patient said, however, that she felt quite comfortable. Hypodermoclysis was carried on during this period at intervals. On July 2, 8 liters of saline solution were thus given. Glucose was given by enema but evidently not absorbed.

The patient's mental condition gradually became more cloudy and stuporous. For twenty-four hours before death the respiratory movements were of quite characteristic air-hunger type. The patient died on the forty-first day after taking the mercury.

Retinal examinations were made on several occasions but no abnormality noted.

The Urine: The amount varied considerably, depending chiefly on fluid intake. The average was about a liter a day, with something over two liters as the high extreme. There was not evident at any time an inability to excrete water by the kidney. There was no edema and in the last week the response to hypodermoclysis was prompt and adequate. The specific gravity of the urine was generally low, rising above 1.015 on two days, and on several being below 1.005. After the first week the amount of albumin was slight and was precipitated almost completely by acetic acid in the cold (nucleo-albumin). The urine contained considerable pus from a cystitis, and usually erythrocytes; but casts of any sort were seldom noted after the first week of the sickness. Mercury was found in all specimens of urine examined until June 21, when the tests were negative.

No study of the chlorid or nitrogen metabolism could be carried out since the ingest was made uncertain by vomiting and the patient was incontinent of urine. Two twenty-four-hour collections of urine secured by means of a retention catheter were analyzed; the sodium chlorid was just under 3 grams and the nitrogen about 6 grams. While these results are probably too low, as some urine was doubtless lost, they do not in themselves suggest a plus balance. This is supported in respect to the chlorid by absence of detectable edema. Considerable interest attaches itself to renal tests in cases of this nature, as the condition presents the essential features of an experimental nephritis in a human subject. A number of phenolsulphonephthalein tests were made and in none was there recovered a detectable amount of the test-substance.

Non-protein nitrogen of the blood was estimated three times; on June 10 it was 225 mg., on the 15th, 209 mg., and on the 26th, 238 mg. Of the last figure, 71 per cent. (176 mg.) was urea.

This history presents some interesting departures from the common course of events in cases of this sort where the duration of life is brief. Anuria was at no time a symptom, and when the amount of urine fell below normal this was adequately accounted for by a low ingestion of fluids. When the water intake was forced there was apparently a normal response in output. In contrast again with the usual picture are the convulsive seizures, muscular twitchings and the toxic psychosis. The stupor and coma that accompanies anuria induced by mercury poison in common with anuria from other causes, is so uniform in its manifestations that Ascoli separated the syndrome from that of uremia under the caption of "urinary poisoning." The salient characteristics in this clinical picture are the progressive lassitude and somnolence, gradually deepening into coma as death approaches. These are the manifestations notable in dogs after the ligation of the renal arteries, and they describe also the nervous symptoms usually evident in cases poisoned with mercuric chlorid.[2] Convulsions are seldom observed and only in the latter hours of life. Of those symptoms which are associated with uremia, there were observed in this case, besides the evidences of renal disease, epileptiform convulsions, muscular twitching and a psychosis of the usual toxic type. Whether this constitutes uremia must be left undetermined.

Further consideration must be based on an anatomical study.

The autopsy disclosed, besides an eroded condition of the lower bowel and degenerative changes in the liver, a remarkable nephritis which was studied with care from many sections. The following note is Dr. Elser's comment on the condition observed.

*Examination of Kidneys.*—Microscopic examination of the kidneys shows dilatation of the tubules of the cortex with extensive degeneration, necrosis and desquamation of the lining epithelium. Many of the convoluted tubules are more or less completely filled with necrotic material which, in places, is the seat of calcific deposits. Some of these masses show small colonies of bacteria. The interstitial structures are edematous and show, in places, small areas of round cell infiltration. Occasional masses consisting entirely of bacteria are found in the vessels and between the convoluted tubules. The fact that the surrounding structures reveal no evidences of reaction suggests that this represents in a large measure a post mortem development of bacteria. The glomeruli are remarkably free from pathologic changes. Slight dilata-

2. It is of interest that Brauer, in his experimental study of the effects induced in the nervous system through poisoning with mercury, mentions that the symptoms he observed might be explained as uremia. The effects he remarked were increased reflexes, ataxia, and paralyses with convulsions as a terminal phenomenon. The worst cases of poisoning showed no nerve changes. Deutsch. Ztschr. f. Nervenh., 1897, xii, 1.

tion of the capsule is seen in places and here and there the epithelial lining is swollen and separated from the subjacent structures. Sudan III preparations show only traces of fat in the epithelial cells of some of the convoluted tubules.

The lesions enumerated above are those usually encountered in the kidney in cases of bichlorid (mercuric chlorid) poisoning.

The lesions noted are remarkably similar to those induced in animals by such poisons as uranium and tartaric acid, in that the damage done is borne chiefly by the tubular epithelium. In this case the evidence of injury was confined more strictly to one structural element — tubules — than in any sections showing experimentally induced renal lesions that have come to my observation. On this account the large non-protein nitrogen of the blood in this case of mercury poisoning is of an especial interest, recollecting that it is with uranium nephritis in animals that this phenomenon also becomes pronounced.

The other consideration that arrests attention is the absence of tangible evidence pointing toward chlorid and water retention. The data available does not permit of conclusion, although the chlorid excretion was as large as the estimated ingest. Edema was not manifest. Considerable water retention may occur, however, before edema can be demonstrated, except by weight, and a "dry" chlorid retention is well recognized. These reservations seem advisable in view of Heinecke's observation that disturbances of chlorid excretion are associated with those poisons which injure the renal tubules.[3]

It is not permissible to build deductions from this scanty material, but better, perhaps, to regard this case as a straw in the wind of evidence.

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3. Relevant to the discussion is a case of mild mercuric chlorid poisoning reported by Monakow since the above was written. Except during the first days of illness, there was no evidence of retention of water or nitrogen. There was, however, chlorid retention and later a minus chlorin balance. Edema was manifest. The poisoning was slight, as the patient recovered without special flushing treatment. Deutsch. Arch. f. klin. Med., 1914, cxv, 227.

# THE OCULOCARDIAC REFLEX

## AN ELECTROCARDIOGRAPHIC STUDY WITH SPECIAL REFERENCE TO THE DIFFERENCES BETWEEN RIGHT AND LEFT VAGAL AND OCULAR PRESSURES IN TABETICS AND NON-TABETICS *

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### INTRODUCTION AND HISTORICAL REVIEW

In 1908 B. Aschner[1] first observed that pressure on the eyeball caused slowing of the pulse and decrease in the depth of respirations. He found that it would arouse stuporous, anesthetized and unconscious patients, and enable them to respond to questions. He also showed that in narcosis the oculocardiac reflex lasts longer than the corneal or pupillary reflexes. Grossmann and Miloslavich[2] in 1912 made similar observations, and Fabre and Petzetakis,[3] working six years later than Aschner, confirmed the observation that the oculocardiac reflex persists even under deep ether or chloroform anesthesia, and can be elicited after the corneal reflex has gone. It was demonstrated by Aschner that the afferent impulse of the reflex passes through the trigeminal nerve to its nucleus in the midbrain, and that the efferent passes by way of the pneumogastric nerve. By cutting the third, fourth, sixth, seventh or eighth cranial nerves he could not destroy the reflex, but by cutting the fifth the reflex was destroyed. He also showed that the inhibition of the heart was not due to increased intracranial pressure, for the relief of pressure by trephining the skull did not abolish the reflex.

Milian,[4] overlooking Aschner's discovery of five years before, stated in 1913 that the phenomenon of pulse-slowing resulting from ocular pressure should be called *"la signe de Gautrelet"* after one of his pupils who had been studying this reflex in his hospital for two years. This

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* From the Hospital of the Rockefeller Institute for Medical Research, New York.

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1. Aschner, B.: Ueber einen bisher noch nicht beschriebenen Reflex vom Auge auf Kreislauf und Atmung, Wien. klin. Wchnschr., 1908, xliv, 1529.

2. Grossmann, J., and Miloslavich, E.: Ueber die Beeinflussung der Herztätigkeit durch Bulbusdruck, Wien. klin. Rundschau, 1912, xii, 177.

3. Fabre and Petzetakis: Persistance du réflex oculo-cardiaque pendant l'anesthésie générale, Compt. rend. Soc. de biol., 1914, lxxvi, 343.

4. Milian: Du ralentissement du pouls radial au cours de la compression oculaire dans la maladie de Basedow, Bull. et mém. Soc. méd. d. hôp. de Paris, 1913, No. 14, p. 878.

would bring back Gautrelet's first observation to three years after Aschner's discovery. Milian found that one could obtain the normal oculocardiac reflex in a dog breathing normally, whether anesthetized or not. But if the thorax were opened and artificial respiration instituted, no slowing of the pulse followed ocular pressure, but instead the tone of the ventricles was increased. This is the experimental evidence for the existence of the reflex and the basis of its mechanism. Many reports dealing with it from a clinical aspect have now been published.

Loeper and Mougeot[5] investigated the condition of the oculocardiac reflex in certain varieties of gastric neurosis, namely, hypervagotonic and the hypersympathicotonic. The former are recognized by the presence of some of the following symptoms: paleness of the face, tendency to myopia, bradycardia, low blood-pressure, moist skin, asthma, gastric hypersecretion, hyperchlorhydria, rapid gastric motility, spasmodic constipation, etc. The latter present the opposite set of symptoms. The former react to pilocarpin with sweating and salivation, but do not react to epinephrin. The latter do not react to pilocarpin, but react to epinephrin with tachycardia, hypertension and glycosuria. They found that the oculocardiac reflex was exaggerated in the hypervagotonic cases and diminished or absent in the hypersympathicotonic. Similar results were obtained in an elaborate investigation by Gautrelet.[6] In several instances they claim to have accelerated the pulse rate by ocular pressure, and they explain this unusual result by stating that the reflex which is generally conveyed by the vagus at times passes over the sympathetic nerve. They consider that an individual whose pulse rate is accelerated or slowed more than ten beats per minute by pressure is abnormal, in the sense that he belongs to one or the other of the two groups named. This is a point to which reference will be made again later.

Lesieur, Vernet, and Petzetakis[7, 8, 9] have studied the condition of the oculocardiac reflex in epileptics. This reflex, as well as tendon and

5. Loeper, M., and Mougeot, A.: Le réflexe oculo-cardiaque dans le diagnostic des nevroses gastriques, Bull. et mém. Soc. méd. d. hôp. de Paris, 1913 No. 14, p. 865.

6. Gautrelet, J.: Le réflexe oculo-cardiaque, Paris méd., Nov. 29, 1913, p. 583.

7. Lesieur, Ch.: Vernet, M., and Petzetakis: Sur un cas d'arrêt total du coeur par réflexe oculo-cardiaque chez un épileptique, Bull. et mém. Soc. méd. d. hôp. de Paris, 1914, No. 9, p. 394.

8. Lesuier, Ch., Vernet, M., and Petzetakis: Contribution à l'étude du réflexe oculo-cardiaque. Son exagération dans l'épilepsie, les variations sous l'influence d'actions médicamenteuses ou toxiques, Bull. et. mém. Soc. méd. d. hôp. de Paris, 1914, No. 9, p. 440.

9. Lesieur, Ch., Vernet, M., and Petzetakis: Considerations sur les modifications des reflexes pendant la compression oculaire chez certains épileptiques, Bull. et mém. Soc. méd. d. hôp. de Paris, 1914, No. 11, p. 510.

cutaneous reflexes, was found to be exaggerated. In their experience it was found that bromid treatment not only lessened the frequency of epileptic attacks, but also diminished the oculocardiac reflex by decreasing vagal irritability. In the same study they found that the right eye responded more strikingly and on slighter pressure than did the left. Usually, when atropin was injected subcutaneously, it abolished the oculocardiac reflex, but ocular pressure continued to inhibit the respiratory motions of the patient just as it did when no atropin was given. This they called the oculophrenic reflex. Later, the same authors[10] found that ocular pressure caused glycosuria in three of their six cases of epilepsy. Four showed albuminuria and all had polyuria. This reflex, they presumed traveled over the sympathetic nerve and not the vagus, because in Claude Bernard's experiments in which he punctured the floor of the fourth ventricle, he observed glycosuria in animals when the vagi were divided, but not when all the sympathetic fibers were cut.

Guillain and Dubois,[11] in a case of double athetosis, noticed that the athetoid movements of the face, tongue and extremities ceased during ocular pressure, but increased during any other medical manipulation. Obstinate yawning and hiccough were observed by Loeper and Mlle. Weil[12] to be influenced favorably by ocular pressure. In six cases of pseudobulbar paralysis, Guillain and Dubois[13] found that four had lost the oculocardiac reflex, and that the other two responded by an acceleration of the pulse rate. The condition of the oculocardiac reflex in various tremors has been studied by Lesieur, Vernet and Petzetakis.[14] Of sixteen cases of Parkinson's disease the reflex was absent in fifteen. Of four cases of multiple sclerosis the reflex was absent in one, accelerated in two and normal in one. The reflex was normal in two cases of alcoholic tremor and in two cases of senile tremor. Of six cases of general paresis the reflex was exaggerated in four and normal

10. Lesieur, Ch., Vernet, M., and Petzetakis: Glycosurie, albuminurie, polyurie provoquées par la compression oculaire, Bull. et mém. Soc. méd. d. hôp. de Paris, 1914, No. 11, p. 515.

11. Guillain, G., and Dubois, J.: Action inhibitrice de la compression oculaire sur les mouvements anormaux dans un cas d'athetose double, Bull. et mém. Soc. méd. d. hôp. de Paris, 1914, No. 16, p. 850.

12. Loeper, M., and Mlle. Weil: Action favorable de la compression oculaire sur certaines manifestations nerveuses et en particulier sur le hoquet, Bull. et mém. Soc. méd. d. hôp. de Paris, 1914, No. 13, p. 631.

13. Guillain, G., and Dubois, J.: L'abolition et l'inversion du réflex oculo-cardiaque dans les paralysies pseudo-bulbaires, Bull. et mém. Soc. méd. d. hôp. de Paris, 1914, No. 12, p. 584.

14. Lesieur, Ch.: Vernet, M., and Petzetakis: Le réflexe oculo-cardiaque chez les sujets atteints de divers tremblements, Bull. et mém. Soc. méd. d. hôp. de Paris, 1914, No. 12, p. 593; Réflexe oculo-cardiaque et maladie de Parkinson, Bull. et mém. Soc. méd. d. hôp. de Paris, 1914, No. 14, p. 599.

in two. They concluded that the oculocardiac reflex might aid in determining whether a nervous lesion was central or peripheral. It does not seem clear, however, how the differentiation is to be made, for a reflex may be either exaggerated or destroyed by a lesion of the afferent limb, center, or efferent limb of a reflex arc. The condition alone of a reflex will scarcely determine the site of a lesion.

In the study of the reflex in organic diseases of the central nervous system, Miloslavich[15] in 1910 was the first to observe that the reflex was absent in tabes dorsalis. Loeper and Mougeot,[16, 17] and Lesieur, Vernet and Petzetakis[18] have shown that in a majority of such patients the pulse rate is either not slowed at all by ocular pressure, or only slightly affected. Lesieur, Vernet and Petzetakis found the reflex to be absent when the Argyll Robertson phenomenon had not yet developed. In syphilis of the nervous system, other than tabes dorsalis, Loeper, Mougeot and Vahram[19] found that the reflex was also absent in thirty of their forty cases.[20] None had Argyll Robertson pupils. These patients were generally in the tertiary stage. The reflex, then, is lost both in tabes and in other syphilitic diseases of the nervous system. But there need be no necessary relation between its loss and the presence or absence of the Argyll Robertson pupil. Different results were obtained in this study concerning the condition of the reflex in syphilitic patients who are not tabetic. Further reference will be made to this later.

The condition of the reflex in Basedow's disease has aroused a great deal of interest. Grossmann and Miloslavich,[2] Milian,[4] Sainton,[21] and Lesieur, Vernet and Petzetakis[14] have shown that it is generally exaggerated in this condition. They attribute this to the hypervagotonicity present in these patients.

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15. Miloslavich, E.: Ueber Trigeminus-vagus Reflex, Wien. med. Wchnschr., 1910, lx, 3051.

16. Loeper, M., and Mougeot, A.: L'absence du réflexe oculo-cardiac dans le tabes, Progrès méd., 1913, No. 52, p. 675.

17. Loeper, M., and Mougeot, A.: Absence fréquente du réflexe oculo-cardiaque dans le tabes, Bull. et mém. Soc. méd. d. hôp. de Paris, 1913, No. 39, p. 942.

18. Lesieur, Ch.: Vernet, M., and Petzetakis: Note sur l'abolition fréquente du réflexe oculo-cardiaque dans le tabes, Bull. et mém. Soc. méd. d. hôp. de Paris, 1914, No. 9, 446.

19. Loeper, M., Mougeot, A., and Vahram: Abolition fréquente du réflexe oculocardiaque chez les syphilitiques, Progrès méd., 1914, No. 14, p. 157.

20. The authors give no reason why the cases should be considered syphilis of the nervous system and not merely tertiary syphilis. They conclude, however, that the frequent absence of the oculocardiac reflex is evidence that the nervous system is early involved.

21. Sainton: Le réflexe oculo-cardiaque dans la syndrome de Basedow, Bull. méd., 1913, No. 60, p. 701.

The condition of the reflex in tachycardias and bradycardias has been studied by Mougeot[22] and Loeper and Mougeot.[23] They believe, in general, that in tachycardias and in bradycardias of nervous origin, the reflex is preserved, while in those of myocardial origin, it is lost. They suggest this difference as a method for distinguishing the two. Fabre and Petzetakis[24] observed that in the bradycardias occurring during the puerperium, ocular pressure caused auriculoventricular dissociation. Dufour and Legras[25] reported the case of a young woman who, having had a miscarriage a few months before, suddenly developed hypo-ovarian symptoms; that is to say, amenorrhea and loss of hair. Later she developed hyperthyroidism, indicated by the presence of exophthalmos and tachycardia. Epileptiform attacks, due, it is said, to cerebrospinal hypertension, supervened. During this time ocular pressure caused no slowing of the heart. Later, when the hair began to return, the reflex reappeared, so that during ocular pressure complete auriculoventricular dissociation took place. No mention was made as to which eye caused the dissociation. The authors do not clearly state whether the reflex was absent before hyperthyroidism developed, during it, or after the symptoms had quieted down. It does not seem likely that the occurrence of hyperthyroidism should make the reflex disappear. Its absence was more probably due to the hyposecretion of the ovaries; for the reflex reappeared when the ovaries functioned normally.

The influence of drugs on the condition of the reflex has been studied by Petzetakis[26] and Mougeot.[27] They found that atropin

22. Mougeot, A.: Tachycardie paradoxale des hypertendus et réflexe oculo-cardiaque, Progrès méd., 1913, No. 51, p. 663; Le réflexe oculo-cardiaque dans les tachycardies permanentes sans arythmie, Compt. rend. Soc. de Biol., 1914, No. 5, p. 205.

23. Loeper, M., and Mougeot, A.: Le réflexe oculo-cardiaque dans le diagnostic de la nature des bradycardies, Compt. rend. Soc. de biol., 1914, No. 3, p. 104.

24. Fabre and Petzetakis: De la bradycardie et automatisme ventriculaire provoqué dans les suites de couches par la compression oculaire, Réunion Obstétrical et Gynecologique de Lyon, January 19, 1914, p. 37.

25. Dufour and Legras: Réflexe oculo-cardiaque provoquant l'arrêt du coeur, l'automatisme ventriculaire et la dissociation auriculo-ventriculaire, Bull. et mém. Soc. méd. d. hôp. de Paris, 1914, No. 14, p. 686.

26. Petzetakis: L'épreuve de l'atropine, du nitrite d'amyl et de la compression oculaire dans les bradycardies totales, Compt. ren. Soc. de biol., 1913, lxxv, p. 677; De l'automatisme ventriculaire provoqué par la compression oculaire et l'atropine dans les bradycardies totales, Compt. rend. Soc. de Biol., 1914, No. 1, p. 15; L'épreuve de la compression oculaire du nitrite d'amyl et de l'atropine dans le diagnostic des bradycardies totales d'origin nerveuse, Presse méd., 1914, No. 17, p. 161; Abolition du réflexe oculo-cardiaque par l'atropine; son exagération par la pilocarpine; sa persistance pendant l'épreuve du nitrite d'amyl, Compt. rend. Soc. de biol., 1914, No. 6, p. 247; Le réflexe oculo-cardiaque chez

0.02 mg.[28] injected subcutaneously abolished the reflex for a period of one to three hours. In a small portion of cases atropin exaggerated the reflex or excited automatic ventricular beats. These are the cases in which atropin retards rather than accelerates the heart rate. Pilocarpin, 0.01 gm. generally exaggerated the reflex. When amyl nitrite was given ocular pressure slowed the accelerated heart, but inhibition began after a longer latent period than occurs normally.

Various studies of the effect of the ocular pressure on the mechanism of the heart itself have been made. Mougeot[29] found that the reflex was generally not abolished during alternation of the ventricle. In some cases of uremia and other intoxications in which ventricular alternation was present, the reflex was lost. Its reappearance was taken to indicate amelioration in the underlying condition. It has been suggested that the loss of the reflex depends on an intoxication of the vagus nuclei in the medulla, by means of which the path of the reflex is cut. In ten of seventy-five cases, Petzetakis[26, 30] obtained transient dissociation of the auricles and ventricles by ocular pressure. The same arhythmia was also observed by Gallavardin, Dufour and Petzetakis.[31] No mention was made of any difference between the effects produced by pressure on the right and left eyes. A little later Petzetakis[32] was able to conclude from a study of two cases that pressure on the left eye is more apt to cause disturbance in auriculoventricular conduction, while pressure on the right eye has a greater influence on rate. His explanation for the difference in effect between the two is that the right vagus is more sensitive than the left. He found two patients in whom ocular pressure caused partial heart-block and later complete auriculoventricular dissociation. The arhythmia was prevented from appearing in these cases by the injection of atropin. Petzetakis[33] reported one case in which atropin had the reverse effect.

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les sujets normaux non bradycardiques, Bull. et mém. Soc. d. hôp. de Paris, 1914, No. 12, p. 562.

27. Mougeot, A.: Supression constante par l'atropine de réflexe oculo-cardiaque, Compt. rend. Soc. de biol., 1914, No. 4, p. 162.

28. This seems to be a small dose.

29. Mougeot, A.: Le réflexe oculo-cardiaque dans l'alternance ventriculaire, Compt. rend. Soc. de biol., 1914, No. 12, p. 541.

30. Petzetakis: Réflexe oculo-cardiaque et dissociation auriculo-ventriculaire, Compt. rend. Soc. de biol., 1914, No. 10, p. 409; Automatisme ventriculaire intermittent provoqué à l'état normal, Bull. et mém. Soc. méd. d. hôp. de Paris, 1914, No. 14, p. 727.

31. Gallavardin, Dufour and Petzetakis: Automatisme ventriculaire intermittent, spontané ou provoqué par la compression oculaire et l'injection d'atropine dans les bradycardies totales, Arch. de mal. du coeur, 1914, vii, 1.

32. Petzetakis: Block auriculo-ventriculaire provoqué par la compression oculaire, Bull. et mém. Soc. méd. d. hôp. de Paris, 1914, No. 14, p. 739.

33. Petzetakis: L'épreuve paradoxale de l'atropine. Son action ralentissante sur le rhythme cardiaque, Bull. et mém. Soc. méd. hôp. de Paris, 1914, No. 12, 567.

In this case the injection *slowed the pulse* and permitted the appearance of the reflex, which had not been present before. In most instances diagnoses of the disorders of the heart mechanism were made by means of polygraphic tracings. This method does not give conclusive information on some points of cardiac arhythmias, and when the tracings are made from patients disturbed by manipulation, they involve some doubt.

Pressure over the vagus nerves in the human subject has been studied particularly by Robinson and Draper.[34] They found that vagal pressure caused slowing of the auricles and ventricles and depressed conductivity in cases having normal hearts. The $Q$-$B^*$ interval, i. e., the time between the $Q$ wave in the electrocardiogram and the footpoint of the brachial pulse, was sometimes diminished. The right vagus had a greater effect on the force and rate of the heart, while the left vagus had a more pronounced effect on the conduction of impulses from auricles to ventricles. The heart was found to respond more quickly to right than to left vagal pressure. Right vagal pressure caused an increase in the action current of the ventricles and a decrease of the current of the auricles, i. e., the height of the $R$ waves was increased and the height of the $P$ waves was diminished. Left vagal pressure diminished the height of the $R$ waves, while the $P$ waves were unaffected. In cases of auricular fibrillation, vagal pressure slowed the ventricles without affecting the auricles. Reference will later be made to these results.

## METHOD

In this investigation, patients were placed in the galvanometer circuit, and electrocardiograms were made to serve as controls. An assistant at the bedside, in continuous telephonic communication with the operator at the galvanometer, exerted pressure on the neck, or on the eye, as the case might be. Enough pressure was exerted on the neck entirely to obliterate the carotid pulse. No accurate measurement of the degree of pressure exerted on the eye was possible. An attempt was made later to determine the amount of pressure, in millimeters of mercury, used on the eyes in order to obtain a standard for comparison with other observers. As nearly as could be judged, a similar degree of pressure was applied to the distended air-tight bag of a blood-pressure apparatus. By this method the pressure employed was found to be approximately 30 mm. of mercury. The eyelid was first closed and the

34. Robinson, G. C., and Draper, G.: Action of Vagus Nerve on Human Heart, Jour. Exper. Med., 1911, xiv, 217; Studies with the Electrocardiogram on the Action of the Vagus Nerve on the Human Heart, Jour. Exper. Med., 1912, xv, 14.

operator's thumb applied under the supraorbital ridge, but not directly over the cornea. The pressure on the two eyes was made as nearly equal as possible. Before pressure was made a strip of curve of seven or eight seconds duration was taken. A signal registered the onset of pressure on the tracings. Pressure continued for about six or seven seconds, the offset being marked by the second signal in the tracing. The exposure was continued about eight or ten seconds longer to include the return of the heart's action to normal. In most cases the second lead was taken (right arm to left leg), but in some instances the first lead (right arm to left arm) was tried, to obtain, if possible, more prominent auricular waves.

Pressure was usually made first on the right vagus, then on the left vagus, then on the right eye and last on the left eye. Two records of each pressure (eight in all) were obtained. Four minutes were permitted to elapse between any two pressures, in order to exclude the summed influence of one on the succeeding. Occasionally, the left vagus was pressed on first and sometimes the left or right eye, to be certain to exclude confusion occasioned by fatigue phenomena. The same patient was in a few instances examined on two different days, and the order of pressure was reversed. Different degrees of pressure were used in the same patient at different times in order to determine whether the amount of slowing varied with the intensity of the pressure. Finally, the symptoms of the patient during pressure were recorded. The signs found included flushing of the face, inhibition of respirations, expressions of pain and the movements of deglutition, etc.

PROTOCOLS[35]

CASE 1.—Schoolboy, aged 9 years. He had a rheumatic history. Pupils react normally.

Clinical Diagnosis: Chorea, rheumatic fever, chronic valvular disease.

CASE 2.—Schoolboy, 11 years old. Pupils react normally.

Clinical Diagnosis: Chronic endocarditis.

CASE 3.—Clerk, 49 years old. No rheumatic history. Pupils react normally.

Clinical Diagnosis: Rheumatic fever, myocardial insufficiency, auricular fibrillation.

CASE 4.—Printer, 49 years old. No rheumatic history. Pupils equal, oval, and react sluggishly to light. Reaction to accommodation is greater and more rapid.

Clinical Diagnosis: Tabes dorsalis.

CASE 5.—Business man, 38 years old. Pupils are equal and react sluggishly to light. Both react well in accommodation.

Clinical Diagnosis: Syphilitic aoritis and syphilis of the spinal cord (syphilitic myelitis).

35. The protocols have been compiled to report the sex, age, occupation, previous diseases having a possible influence on the cardiovascular system, the state of the pupils at the time of examination, and the clinical diagnosis.

CASE 6.—Male, 49 years old. Instructor in physical culture. Pupils are equal, small, do not react to light, prompt reaction in accommodation.

Clinical Diagnosis: Tabes dorsalis.

CASE 7.—Coachman, 45 years old. Pupils unequal, right is 2 mm., left is 5.5 mm. in diameter. Neither reacts to light and both have sluggish reaction in accommodation.

Clinical Diagnosis: Syphilis of the brain and spinal cord (probably early paresis or taboparesis).

CASE 8.—Salesman, 46 years old. Pupils unequal, right slightly larger than left. Both irregular. React slightly but sharply to light and normally in accommodation.

Clinical Diagnosis: Tabes dorsalis.

CASE 9.—Blacksmith, 58 years old. Rheumatic fever four years ago. Hard chancre thirty years ago. Pupils react normally.

Clinical Diagnosis: Acute rheumatic fever, acute pericarditis, cardiac arhythmia, transitory auricular fibrillation, serofibrinous pleurisy and latent syphilis.

CASE 10.—Laborer, 31 years old. Rheumatic fever seven years ago, and two attacks since. Pupils react normally.

Clinical Diagnosis: Chronic valvular disease.

CASE 11.—School girl, 11 years old. Had one attack of rheumatic fever. Pupils react normally.

Clinical Diagnosis: Chronic mitral regurgitation. Chronic cardiac hypertrophy and dilatation.

CASE 12.—School girl, 9 years old. Rheumatic fever five years ago. Pupils react normally.

Clinical Diagnosis: Acute rheumatic fever, chronic valvular disease, mitral regurgitation, aortic regurgitation and aortic stenosis.

CASE 13.—School boy, 12 years old. Pupils react normally.

Clinical Diagnosis: Chronic valvular disease, mitral regurgitation and stenosis, chronic cardiac hypertrophy and dilatation.

CASE 14.[36]— Tailor, 30 years old. Right pupil larger than left. Reaction to light and accommodation is active in both eyes.

Clinical Diagnosis: Secondary syphilis, syphilitic periostitis of the frontal bone, periostitis of ulna; multiple, gonorrheal, periurethral abscesses.

CASE 15.—School boy, 14 years old. Rheumatic fever. Pupils react normally.

Clinical Diagnosis: Acute rheumatic fever and acute endocarditis.

CASE 16.—School girl, 11 years old. Chorea and rheumatic fever. Pupils react normally.

Clinical Diagnosis: Lobar pneumonia.

CASE 17.—Male, 9 years old. School boy. No history of rheumatic fever. Pupils react normally.

Clinical Diagnosis: Lobar pneumonia and empyema.

CASE 18.—Cloakmaker, 40 years old. Pupils slightly dilated and unequal. Left is 4.5 mm., right is 4 mm. in diameter. Both irregular and react in accommodation but not to light.

Clinical Diagnosis: Tabes dorsalis.

CASE 19.—Bookkeeper, 63 years old. No history of rheumatic fever. Pupils equal and react in accommodation but not to light.

Clinical Diagnosis: Tabes dorsalis.

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36. Case 14 has been omitted because he began to show signs of early tabes, although the oculocardiac reflex was present.

CASE 20.—Electrician, 32 years old. Pupils unequal. Right is twice the size of the left. Both react slightly to light and well in accommodation.
Clinical Diagnosis: Tabes dorsalis.

CASE 21.—Business man, 26 years old. Rheumatic history eight years ago. Pupils slightly irregular in outline but react normally.
Clinical Diagnosis: Secondary syphilis. Syphilis of cerebrospinal meninges.

CASE 22.—Girl, 17 years old. Machine operator. Pupils react normally.
Clinical Diagnosis: Diabetes mellitus.

CASE 23.—Man, 53 years old. Actor. Pupils are unequal; right 3 mm., left 2.25 mm. in diameter. Neither reacts to light, but both react in accommodation.
Clinical Diagnosis: Tabes dorsalis.

CASE 24.—Reporter, 34 years old. Pupils are equal, irregular in outline, react normally to light and in accommodation.
Clinical Diagnosis: Secondary syphilis, syphilis of the cerebrospinal meninges, syphilis of the auditory and facial nerves.

CASE 25.—Tailor, 53 years old. Pupils equal, slightly irregular, do not react to light; both react slightly in accommodation.
Clinical Diagnosis: Tabes dorsalis.

CASE 26.—Porter, 35 years old. Pupils react normally.
Clinical Diagnosis: Lobar pneumonia and lung abscesses.

CASE 27.—Boy, 18 years old. Factory hand. Pupils react normally.
Clinical Diagnosis: Lobar pneumonia.

CASE 28.—Salesman, 24 years old. Pupils react normally.
Clinical Diagnosis: Lobar pneumonia.

CASE 29.—Diamond cutter, 60 years old. Had syphilis thirty-eight years ago. Pupils are somewhat dilated. Left does not react to light as completely and quickly as right. Both react well in accommodation.
Clinical Diagnosis: Transient heart-block. Syphilis of the heart.

CASE 30.—Farm hand, 26 years old. Pupils react normally.
Clinical Diagnosis: Acute rheumatic fever, acute myocarditis, lobar pneumonia.

## GENERAL RESULTS AND OBSERVATIONS

The material for this study consisted of eight cases of tabes dorsalis, one case of taboparesis, five cases of syphilis which were non-tabetic, nine cases of chronic endocarditis (having a normal rhythm), one case of chronic endocarditis with auricular fibrillation, five cases of lobar pneumonia, and one case of diabetes mellitus. The five non-tabetic syphilitics included two cases of syphilis of the cerebrospinal meninges, one of syphilitic myelitis, one of syphilis of the heart, and one patient who has been observed during the secondary stage and who now suggests signs of early tabes.

The results of ocular and vagus pressure from four (Cases 4, 18, 20 and 25) of the eight cases of *tabes dorsalis* are shown in detail in figures 1a-d. Figure 1a gives the results of right vagus pressure, 1b of right ocular pressure, 1c of left vagus pressure and 1d of left ocular pressure. In one instance (Figure 1c, Tracing 157) there is marked slowing on vagus pressure. The degree of inhibition of the heart produced by vagus pressure was greater in this case than in any of the

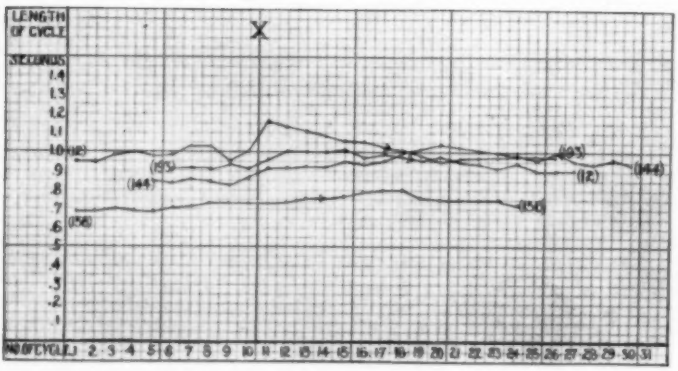



Figure 1a

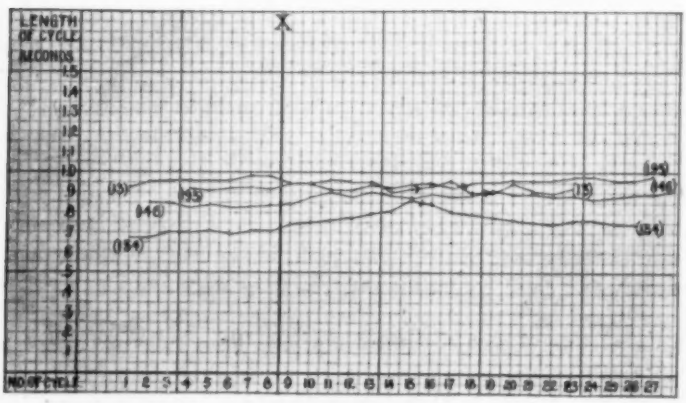



Figure 1b

Figures 1, 2, 3 and 4 detail the duration (on the ordinate) of every cardiac cycle (on the abscissa) calculated from electrocardiograms taken during a given digital (vagal or ocular) pressure. X indicates the onset of pressure; the arrow (→) the time of the offset. The figures marked *a* show the results

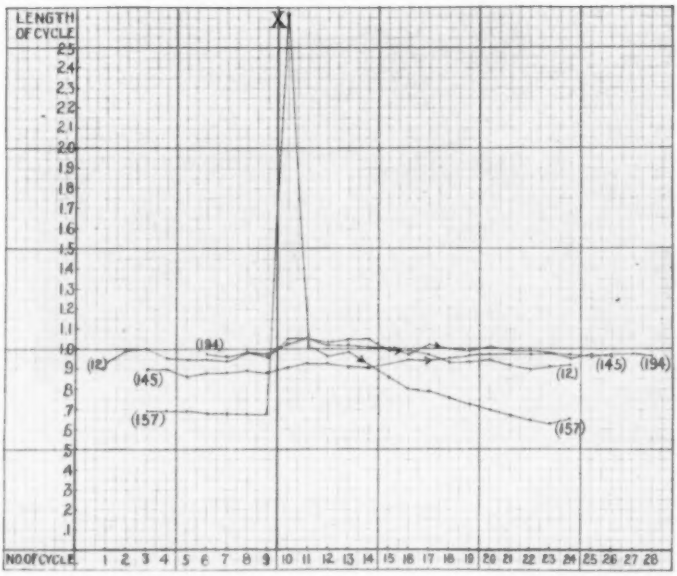



Figure 1c

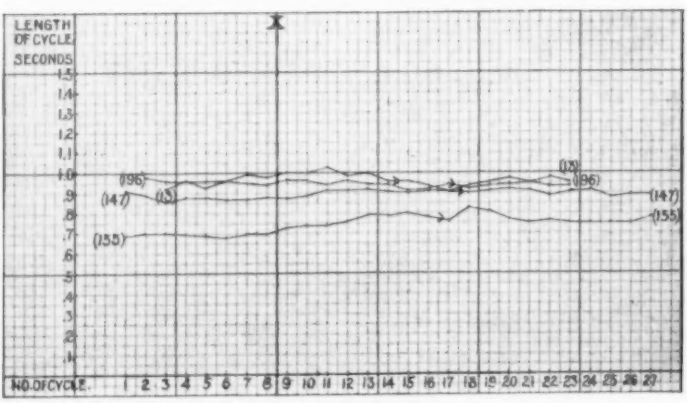



Figure 1d

of right vagus pressure: *b*, right ocular pressure; *c*, left vagus pressure; *d*, left ocular pressure. The numbers at the beginnings and ends of the curves indicate, in the accompanying table, the patients to whom the records refer.

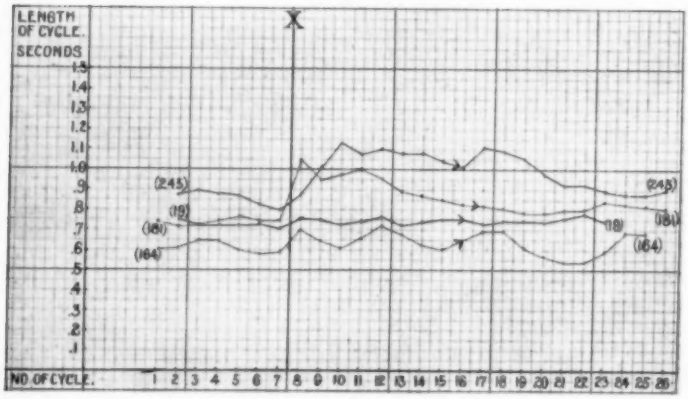



Figure 2a

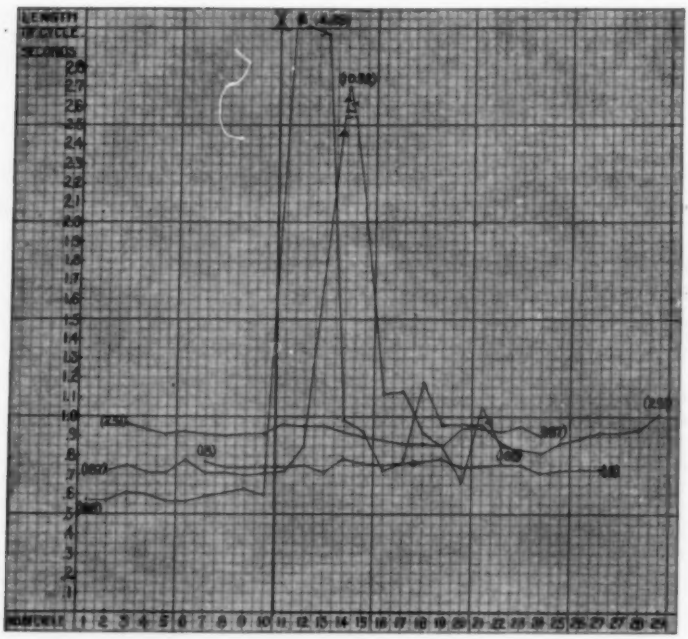
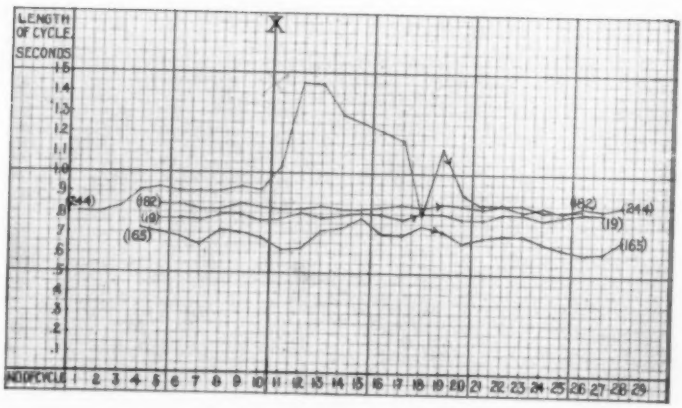


Figure 2b

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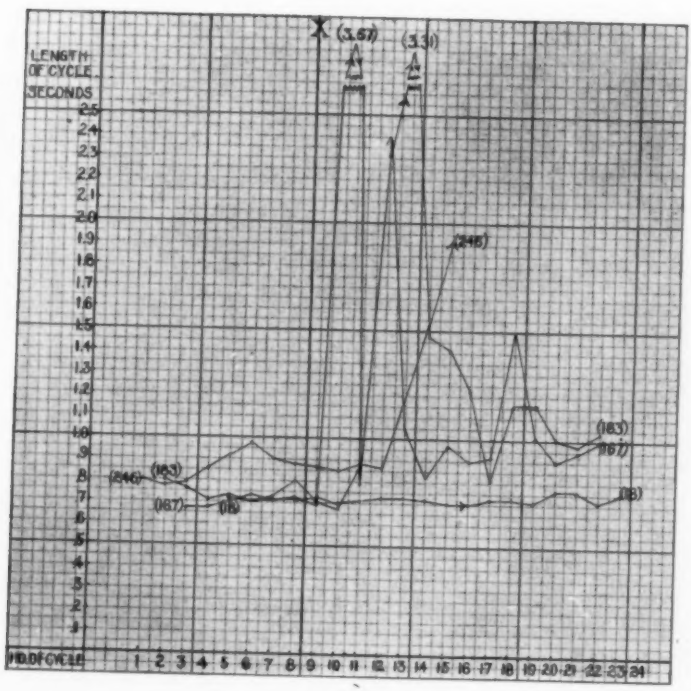


Figure 2d

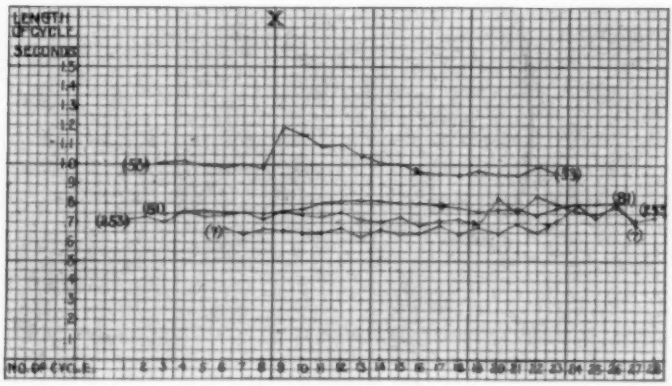


Figure 3a

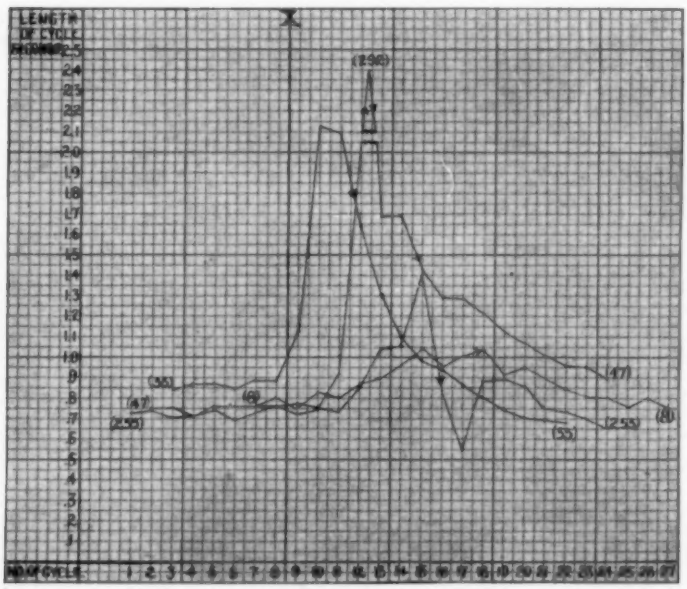


Figure 3b

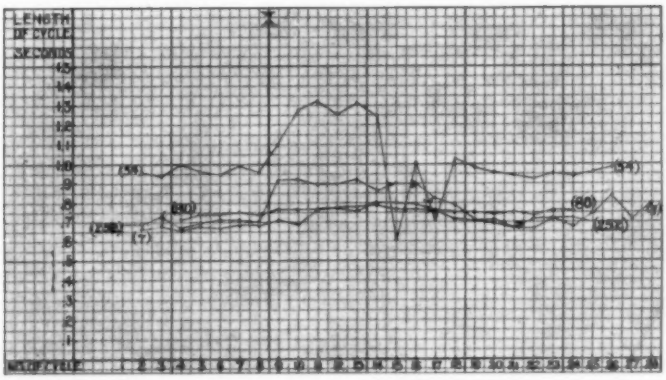


Figure 3c

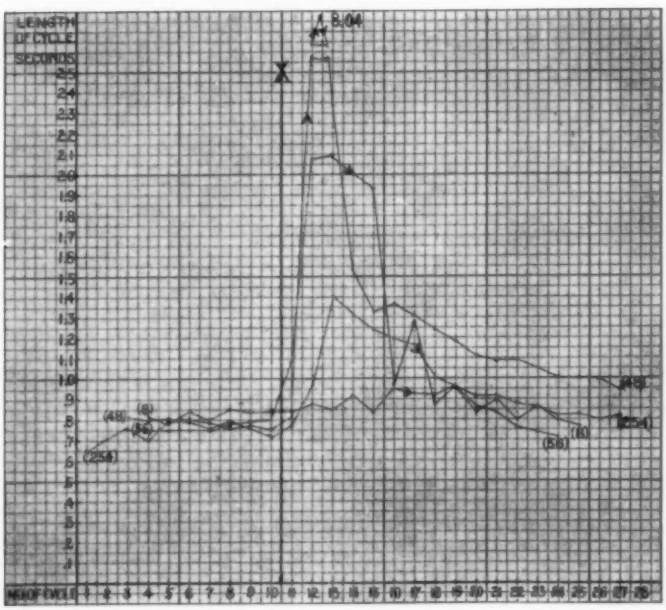


Figure 3d

other cases (tabetic or non-tabetic.)[37] This is a significant point, because although the oculocardiac reflex will be shown to be generally absent in tabetics and present in non-tabetics, the greatest degree of slowing by direct vagal pressure was obtained in a tabetic. The centrifugal path of the reflex was intact. One (Case 6) of the tabetics, whose pupils were rigid and did not react to light, developed a moderate amount of slowing as a result both of right and left ocular pressure. In some of the other tabetics, where the oculocardiac reflex was absent, the pupils reacted slightly to light. All the other tabetics gave no slowing on ocular pressure. In eight cases of tabes dorsalis, then, one showed a moderate oculocardiac reflex whereas it was absent in the other seven. There is, also, no exact parallelism between the Argyll Robertson reaction and the oculocardiac reflex. There was no

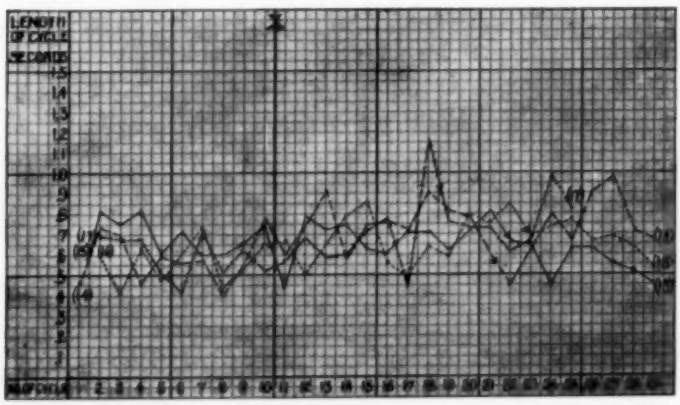

Figure 4a

Figure 4.—a and b give the results of pressure in a case (No. 3) of auricular fibrillation, before (a) and during (b) the administration of digitalis; a 14 + b 201 —— —— —— right vagus; a 15 + b 208 ——— right eye; a 16 + b 202 — — — — left vagus; a 17 + b 209 x——x——x left eye.

difference in the effect produced by pressure on the two eyes. The only change noticed in the electrocardiograms was a slight increase in the prominence of the *P*-waves in two instances on right vagal pressure. There was no marked change in the conduction time or in the form of the ventricular complex.

In the second group of cases are included the four *syphilitics*[38] who were *not tabetic*. (Figs. 2a-d.) In three of the four cases, the oculo-

37. The term non-tabetic is used throughout to include all the cases in the series except those of tabes dorsalis.

38. Case 14, originally included here, has been omitted because he began to show signs which may be those of early tabes, although the oculocardiac reflex was present.

cardiac reflex was preserved. The results obtained here differ, therefore, from those obtained by Loeper, Mougeot and Vahram.[19] They found that in 75 per cent. of their cases of syphilis the oculocardiac reflex was *absent*. The reflex was *present* in 75 per cent. of the cases in this study. In two (Cases 21 and 24) of the four cases (Fig. 2b, Tracings 166 and 187, and Fig. 2d, Tracings 167 and 183) there was complete inhibition of the heart for periods ranging from 3.31 seconds to 10.92 seconds (Fig. 5). In a third case (No. 29) there was a moderate amount of slowing, that is to say, a slight reaction. The fourth (Case 5) did not react at all to ocular pressure. This case was one of syphilis of the spinal cord and syphilitic aortitis. He showed an Argyll Robertson pupil, so that it is not at all unlikely that he had early tabes. The slowing in these cases was more pronounced during pressure on the right

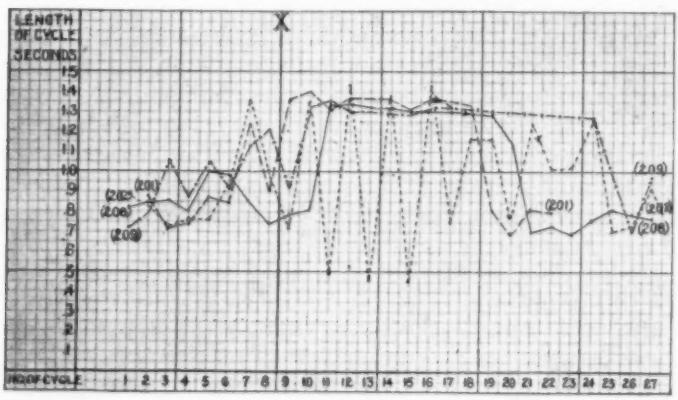


Figure 4b

ocular bulb than on the left. There were no changes in the electrocardiograms. In Case 21 an escaped ventricular beat occurred 0.79 second after the preceding pause of 3.67 seconds. Another long pause of 2.40 seconds followed. The escaped ventricular beat was of normal form, probably supraventricular in origin. In this case all the waves were greatly diminished in height during ocular pressure, so that it was difficult to differentiate a ventricular contraction from the oscillations that are sometimes observed in electrocardiograms during stimulation of the vagus nerves. Case 24 was very sensitive to ocular pressure. The pacemaker was entirely inhibited by right ocular pressure for 10.92 seconds (Fig. 5). Auriculoventricular conduction was lengthened considerably during pressure on the left eye. The effect on conduction, however, was not limited to pressure on the left eyeball, for the P-R time following the pause of 10.92 seconds was 0.24 second.

The results of vagal and ocular pressure were also studied in five cases of *pneumonia* (Cases 17, 26, 27, 28, 30). The curves plotted from electrocardiograms taken during vagal pressures rose very slightly, that is to say, pressure did not slow the heart very much. The curves of ocular pressure, on the other hand, rose abruptly after a latent period of from one to three beats. This demonstrates strikingly how much more effective ocular pressure is in slowing the heart than direct vagal pressure. Another point to be observed is that the pulse rate did not drop back to normal after pressure was released, but in fact was still quite slow after ten seconds, and in some instances after thirty seconds. This occurrence emphasizes the importance of waiting between succeeding pressures on the same patient, to guard against either fatigue phenomena or summation of stimuli. One of the pneumonia patients, Case 17, showed only slight slowing. The reason for this is, probably, that not enough pressure was exerted.

Three (Cases 17, 28 and 30) of the five pneumonia cases showed no changes in the form or sequence of the curves, except the slowing. In the other two, several interesting changes were observed. In Case 26 left ocular pressure caused considerable delay in conduction time. In places auricular waves cannot be distinguished at all, and yet the ventricular complexes are of normal contour. The auricular representation is iso-electric.

The last of the pneumonia cases (No. 27) presented varied changes during ocular pressure. Figure 8 shows three inverted *P*-waves, one of which was blocked. (Inverted *P*-waves were seen in one other instance during left ocular pressure.) The same tracing showed a conduction time of 0.28 second. On five different occasions left ocular pressure caused delayed conduction, the *P-R* interval rising to 0.24 and 0.32 second. In none of the four times when the right eye was pressed in this case was there any delay in conduction. Figure 6 shows partial heart-block as a result of left ocular pressure. Finally, in one instance, pressure on the left bulb caused an increase in the height of the *P*-waves, an occurrence observed also by Robinson and Draper[34] as a result of direct pressure on the left vagus nerve. In this case, then, right ocular pressure merely slowed the heart and had no effect on conduction. Pressure on the left eye, however, caused ectopic auricular contractions, delayed conduction, partial heart-block, and an increase in the height of the *P*-waves. These different effects appeared in the same individual under similar circumstances. It seems reasonable to believe that the duration and the force of the pressure, which must have varied, were important factors in determining the degree of inhibition that took place. Just as increasing strengths of faradic currents applied

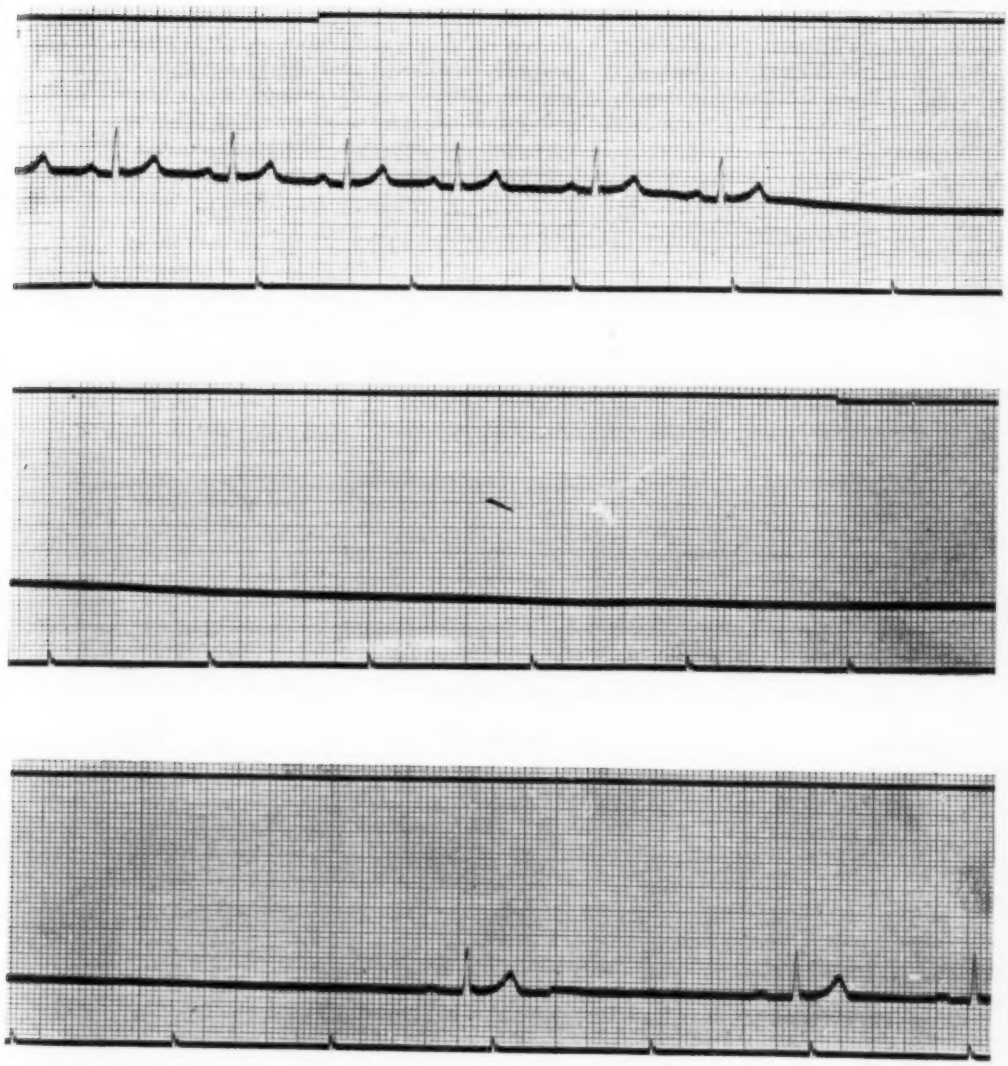

Fig. 5.—Case 24. Right ocular pressure. An electrocardiogram showing total inhibition of all chambers of heart for 10.92 seconds. The *P-R* time of the beat after the long pause is lengthened to 0.24 second. The slowing continued for twenty-four seconds after the release of pressure. In all curves, divisions on the abscissa equal 0.04 second. Above is a signal indicating the duration of digital pressure. Below a time signal marking one-second intervals.

to exposed nerves in experiments on animals are accompanied by increasing effects, so may increasing pressures produce increasing effects on the rate and on conduction. Mild pressures may slow the rate and perhaps slightly affect conduction; slightly greater pressures may block auricular beats, and great pressures may stop the heart. Under certain circumstances, possibly during removal of the pressure, complete auriculoventricular dissociation might occur. It is therefore important to standardize the degree and duration of pressure. In addition, the resistance offered by the eye is probably a factor involved in eliciting the reflex.

Nine cases of *chronic valvular disease* (Patients 1, 2, 9, 10, 11, 12, 13, 15, 16), all of whom had hearts actuated by a normal rhythm, were studied. Figures 3a-d show the results in four of them (1, 2, 9 and 10). Only one (Case 10) of the nine cases had a moderate reaction to *vagal pressure*, while another (Case 1) showed a slight effect. All the others were little, if at all, affected by either right or left vagal pressure.

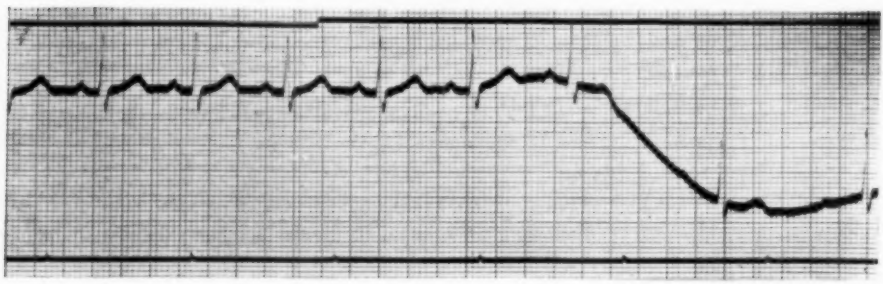

Figure 6

Fig. 6.—Case 27. Left ocular pressure. Moderate slowing of the heart is shown. There is a decrease in the size of the *P* wave. Conduction time is delayed and is gradually increased until an auricular beat is blocked. The *P-R* interval following the blocked beat is short, 0.15 second.

On *ocular pressure*, eight (Nos. 1, 9, 10, 11, 12, 13, 15 and 16) reacted strikingly, and the other one (No. 2) moderately. The patient (No. 2) who reacted with moderate slowing was not pressed very vigorously; he was one of the first patients studied. The first (No. 1) patient studied showed no slowing whatever on moderate ocular pressure, but on greater pressure he had a good reaction. In this case *P*-waves diminished in height during right ocular pressure, and during left ocular pressure *P*-waves were blocked. Left ocular pressure caused delayed conduction (P-R interval 0.44 second in one instance). Right vagal pressure caused a slight delay in conduction on one occa-

sion. There was no noticeable difference on the heart rate between the effects of right and left ocular pressure in these cases.

The results observed in one patient (Case 3) whose heart showed the rhythm of *auricular fibrillation* are included in the study. Observations were made before and during the administration of digitalis. Figure 4a shows the results of ocular and vagal pressures before digitalis was given. There was no evidence of slowing during pressure. Figure 4b, which gives the results after a course of digitalis therapy, shows a distinct slowing on pressure. There was no difference in effect between the right and left sides or between ocular and vagal pressure either before or during digitalis treatment. All other non-tabetic cases showed a distinct difference in reaction between ocular and vagal pressure. Many of them manifested differences in the effect of pressure on the right and left eyes. But here the result was the same whether ocular or vagal pressure was exerted or whether it was the left or right side that was used. The up and down swings in Figure 4b, Curve 202,

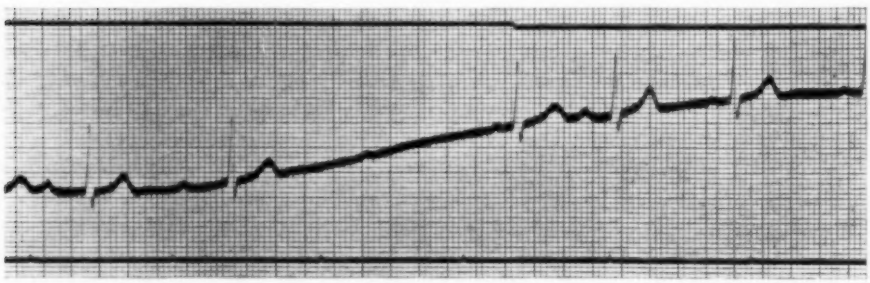

Figure 6—Continued

are due to three premature ectopic ventricular beats alternating with the normal ventricular contractions. There is a striking tendency for all normal heart cycles in this chart to be of the same length during pressure. Digitalis, it seems, changed the condition of the oculocardiac reflex. Wenckebach[39] and v. Hoesslin[40] have similarly shown that digitalis produces a heightening of the efficiency of vagus pressure.

One case of diabetes mellitus was studied (Case 22). Tracings were taken two different times at an interval of fifteen days. At neither time was there more than the slightest slowing either during vagal or ocular pressure. There has been no report in the literature of the condition of the oculocardiac reflex in this disease. A study

39. Wenckebach, K. F.: Die Unregelmässige Herztätigkeit und ihre klinische Bedeutung, W. Engelmann, Leipzig and Berlin, 1914, p. 172.

40. Von Hoesslin, H.: Beobachtungen über den Einfluss des Vagus auf das menschliche Herz, Deutsch. Arch. f. klin. Med., 1914, cxiii, 537.

of more cases is required to decide whether the condition of the reflex found in this case is typical.[41]

The sensations experienced and the objective signs displayed during pressure have been studied to determine if differences between tabetics and non-tabetics were present, and to see if they were constant. Of the thirty patients studied, six had unusual sensations of one kind or another (Table 1). The others felt nothing but the pressure and the pain, when there was any. An examination of Table 1 shows that *vagus pressure* had little effect on either tabetics or non-tabetics. Occasionally a patient complained of slight pain; very rarely there was flushing or inhibition of respiration; on a few occasions the patient swallowed during or immediately after pressure. Deglutition might very well have resulted from the discomfort of the pressure on the neck. *Ocular pressure*, on the other hand, produced a marked difference in the two groups of cases. In the tabetics, three[42] had a moderate amount of pain (marked +), three had a slight or very slight pain (marked v. sl.) and three had no pain whatever (marked —). In five cases there was slight flushing and in four none at all. Respiration was checked during pressure on only two occasions and at no time was there any impulse toward swallowing. In contrast to this are the results in non-tabetics. The pain from ocular pressure was quite severe in all but two cases. One of these was a case of syphilitic myelitis (there is evidence that he is developing tabes), and the second was subjected to much lighter pressure than any of the others. There was flushing of the face in all but two cases. Respiration was checked in fifteen of the twenty cases. It is evident that pain, flushing of the face and respiratory inhibition generally occur during ocular pressure in non-tabetics, and to a much less extent in tabetics.

## DISCUSSION AND SUMMARY

The oculocardiac reflex (inhibition of the heart produced by ocular pressure) is a normal but variable reflex. The statement that a heart is abnormal if its rate is slowed or accelerated by more than ten beats a minute, made by Loeper and Mougeot[5] is not substantiated by the observations made in this study. Some individuals normally have a more active oculocardiac reflex than others, just as some have more active tendon and superficial reflexes. In fact, when the reflex is con-

41. Since these observations were made, three cases of diabetes in the medical wards of the Peter Bent Brigham Hospital were investigated. In one case the oculocardiac reflex was absent on two different occasions. In the other two there was a moderate slowing on right ocular pressure, but none on the left.

42. I have included under tabetics Case 7, which is probably a case of early tabo-paresis.

TABLE 1.—Sensations Elicited by Pressure in Tabetics and Non-Tabetics

TABETICS

| Case | Vagus | | | | Eye | | | | Subjective Symptoms |
|---|---|---|---|---|---|---|---|---|---|
| | Pain | Flushing | Inhibition of Respiration | Deglutition | Pain | Flushing | Inhibition of Respiration | Deglutition | |
| 4 | — | + | — | + | + | sl. | — | — | Felt slight pain with ocular pressure, especially right. |
| 6 | — | — | — | — | — | — | — | — | Felt nothing but the pressure. No pain. |
| 7 | — | — | — | — | + | — | — | — | Slight pain in eyes. Pins and needles sensation in right eye. |
| 8 | — | — | — | — | — | — | — | — | Had no other feeling than that of pressure. |
| 18 | — | — | + | — | — | sl. | — | — | Merely felt pressure. |
| 19 | — | — | — | — | sl. | sl. | + | — | Merely felt pressure. |
| 20 | — | + | — | — | + | sl. | — | — | Pressure on left vagus made him feel faint. |
| 23 | — | — | — | — | vsl. | — | — | — | Felt nothing except slight pain in eyes. |
| 25 | — | — | — | — | sl. | sl. | — | — | Felt very slight pain in the eyes. |

NON-TABETICS

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 1 | — | — | — | — | + | + | — | + | Pain in the eyes. |
| 2 | .. | .. | .. | .. | .. | .. | .. | .. | No record obtained. |
| 3 | — | sl. | — | — | ++ | + | — | — | Felt faint, choking sensation, cramp in belly when eyes were pressed. |
| 5 | — | — | — | — | — | — | — | — | Felt nothing peculiar. (See protocol.) (May be tabetic.) |
| 9 | — | + | — | — | ++ | + | + | — | Felt nothing but pain from pressure on eyes. |
| 10 | — | — | — | — | ++ | + | + | — | Felt nothing but pain from pressure on eyes. |
| 11 | — | — | + | — | ++ | — | + | — | Felt nothing but pain from pressure on eyes. |
| 12 | — | — | — | — | ++ | + | + | — | Felt nothing but pain from pressure on eyes. |
| 13 | + | + | + | — | ++ | + | + | — | Felt nothing but pain from pressure on eyes. |
| 14 | — | — | — | + | ++ | + | + | — | Felt nothing but pain from pressure on eyes. |
| 15 | — | — | — | — | ++ | + | + | — | Felt nothing but pain from pressure on eyes. |
| 16 | — | — | — | — | ++ | + | + | — | Felt nothing but pain from pressure on eyes. |
| 17 | + | — | — | — | ++ | + | + | — | Felt nothing but pain from pressure on eyes. |
| 21 | rt. | rt. | | | | | | | |
| | + | + | — | — | ++ | + | + | — | Felt nothing but pain from pressure on eyes. |
| 22 | — | sl. | — | — | ++ | + | + | — | Felt nothing but pain from pressure on eyes. |
| 24 | — | — | — | — | ++ | + | + | — | Felt slow electric current going through body when eyes were pressed. It caused him much pain. |
| 26 | — | — | — | — | ++ | + | + | — | Left eye pained more than right. |
| 27 | — | — | — | — | ++ | + | + | — | Left eye pained more than right. |
| 28 | — | — | — | — | ++ | + | + | — | Felt nausea when right eye was pressed, in addition to pain. |
| 29 | — | — | — | — | ++ | + | — | — | Merely felt pain. |
| 30 | — | — | — | — | ++ | + | — | — | When right eye was pressed right leg felt dead and it lifted itself up from bed. |

sidered absent there is often a slight inhibition of the heart, as is shown by a tendency for the curves in Figures 1b and 1d to rise during pressure. It seems highly probable that different effects may be produced in the same individual by changing the duration and the degree of ocular pressure. This is shown in several cases described in this investigation. The comparison which was instituted made it clear that inhibition of the heart could much more easily be obtained by ocular than by direct vagal pressure. A difference as striking as that which has been observed between the two can only be obtained if the eyes are pressed quite firmly, causing the patient slight distress. Ocular pressure brings out disturbances in the heart mechanism which were not obtained by direct vagal pressure.

The reflex was found to be generally absent in tabes dorsalis. The cause for this probably is a lesion in the brain itself. Although in all the cases of tabes the pupils were inactive to light or reacted sluggishly,

Figure 7

Fig. 7.—Case 26. Right ocular pressure. Total inhibition of the heart for periods of 2.27 seconds to 3.65 seconds is shown. *P*-waves are entirely absent; the ventricular complexes are of normal form. Beat V is an escaped ventricular contraction of normal form.

there does not seem to be any constant relation between the occurrence of the Argyll Robertson phenomenon and the loss of the oculocardiac reflex. In fact, the only tabetic who had a moderate oculocardiac reflex, had no pupillary reaction to light whatever. These findings in tabetics are in accord with the results obtained by previous investigators. Tabetics do not complain of pain on ocular pressure to the same extent as non-tabetics, nor do flushing of the face and periods of apnea during pressure occur to as great a degree as in non-tabetics. It is not impossible that these reflex phenomena result from the sensation of pain. Of the five cases of syphilis (Cases 5, 14, 21, 24 and 29), if those patients are excluded who might possibly be developing tabes, namely, Cases 5 and 14, then three, or 100 per cent., had a normal oculocardiac reflex; and if the other two are included, all but one, Case 5, or 80 per

cent., reacted normally. These results differ decidedly from those of Loeper, Mougeot and Vahram,[19] who found the reflex absent in 75 per cent. of their cases. One case of diabetes mellitus and one case of auricular fibrillation were found to have no oculocardiac reflex. No explanation for its absence can be given in the case of the diabetic. The patient with auricular fibrillation reacted after he was given digitalis. Of all the other cases in this series (including nine cases of chronic valvular disease, five of pneumonia, and five of syphilis) only one (Case 5) did not have an oculocardiac reflex, and he had signs of early tabes.

In tabetics there was no difference between the effects of pressure on the two eyes. In non-tabetics there was a distinct difference. The right reflex had a slightly greater effect on auricular contraction.[43] The different grades of inhibition caused by right ocular pressure were, first, a diminution in the height of the *P*-waves with only mod-

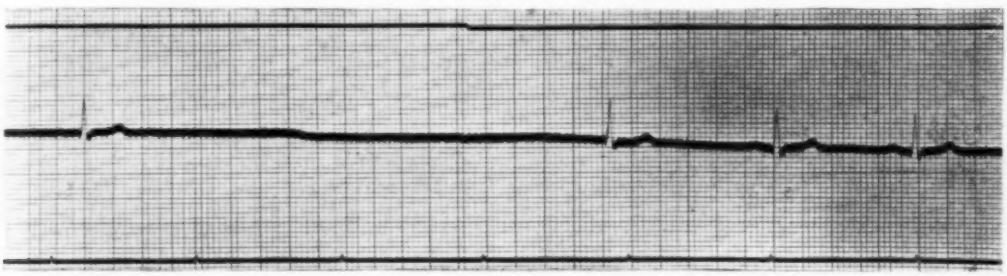

Figure 7—Continued

erate slowing; second, disappearance of the *P*-waves and slowing of the rate of the ventricular contractions; third, complete inhibition of all the chambers of the heart. Left ocular pressure, on the other hand, may cause similar phenomena, but does not do so as often as right. The *P*-waves frequently could not be identified, but after pressure was released they gradually reappeared (Fig. 7). The ventricular representative, *R*, continued to have a normal form even though the ventricular rate was reduced. It is impossible in these cases to say whether the normal pacemaker was completely inhibited or whether the origin of the impulse for ventricular contractions resided in the junctional tissue. In most instances the pacemaking function probably continued to be at the sinus node. In any case the impulse was supraventricular in origin, for the form of the ventricular complexes remained normal.

43. The greater slowing seen in the charts of pressures on the left side is only apparent and not real; it depends on the blocking of auricular beats which were slowed less by left than by right sided pressures. Rates, however, are counted from ventricular contractions.

The change in the mechanism of the heart beat caused particularly by left ocular pressure were delayed conduction, partial heart-block and inversion of the *P*-waves. Complete inhibition of all the chambers of the heart also occurred. Ectopic ventricular beats occurred in two cases during left ocular pressure. Accurate measurements of the heights of the *P*- and *R*-waves before and during ocular or vagal pressure were not made. *P*-waves diminished in height in many instances during both left and right ocular pressure. One case showed a decrease in the height of the *P*-waves even before slowing of the heart began.

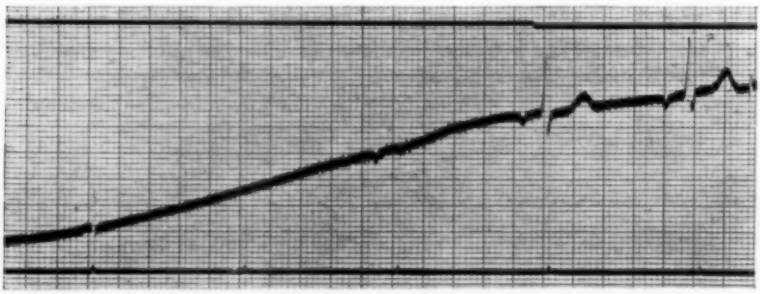

Fig. 8.—Case 27. Left ocular pressure. Inhibition of the ventricle is shown. Three inverted *P*-waves occurred one of which was blocked; in the other two the *P-R* time is short. After release from pressure the *P-R* time was 0.32 second.

Occasionally the height of the *P*-wave was increased by left ocular pressure.

Differences between right and left oculocardiac reflexes, such as were obtained by stimulation of the left and right vagus, were not as

TABLE 2.—PATIENTS REFERRED TO IN THE CURVES

| Patient 4 | Patient 18 | Patient 20 | Patient 25 | Patient 5 | Patient 21 | Patient 24 | Patient 29 | Patient 2 | Patient 10 | Patient 9 | Patient 1 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Fig. | | | | Fig. | | | | Fig. | | | |
| 1a 12 | 144 | 156 | 193 | 2a 19 | 164 | 181 | 245 | 3a 7 | 53 | 81 | 253 |
| b 13 | 146 | 154 | 195 | b 18 | 166 | 187 | 251 | b 8 | 55 | 47 | 255 |
| c 12 | 145 | 157 | 194 | c 19 | 165 | 182 | 244 | c 7 | 54 | 80 | 252 |
| d 13 | 147 | 155 | 196 | d 18 | 167 | 183 | 246 | d 8 | 56 | 48 | 254 |

definite and striking as those obtained in experiments by Cohn.[44] The fact that these differences were not so clearly demonstrated in the oculocardiac reflex must be due to the more complicated pathway pur-

44. Cohn, A. E.: On the Differences in the Effects of Stimulation of the Two Vagus Nerves on Rate and Conduction of the Dog's Heart, Jour. Exper. Med., 1912, xvi, 732.

sued by the impulses through the brain. According to the experiments referred to, the right vagus has a greater influence on the pacemaker and the left a greater influence on auriculoventricular conduction. The difference between pressure on the two eyeballs compares satisfactorily, however, with that found by Robinson and Draper[34] in their vagus experiments.

## CONCLUSIONS

1. Ocular pressure affords a simple and safe method of obtaining reflex vagus inhibition of the heart.

2. Inhibition of the heart by the oculocardiac reflex is much more profound and more frequently obtained than by pressure over the vagus nerves.

3. The oculocardiac reflex is generally absent in tabes dorsalis, present in pneumonia, syphilis (non-tabetic) and chronic valvular disease.

4. The reflex was absent in one case of diabetes mellitus and also in one case of auricular fibrillation before digitalis treatment. It was present after digitalis was given.

5. Right ocular pressure has a slightly greater effect on the rate of the heart than left. It may stop the heart for a long period of time, relatively speaking, the *P*-waves are sometimes diminished in size and may become iso-electric. Occasionally the auriculoventricular interval is lengthened.

6. Left ocular pressure has a much greater effect on the conduction mechanism of the heart than right. It may lengthen auriculoventricular conduction, cause partial heart-block and result, possibly, in automatic ventricular rhythm. On two occasions inverted *P*-waves were seen. The height of the *R*-waves is sometimes increased, at other times diminished. Ectopic ventricular beats were twice observed. The *P*-waves are often diminished in size, but occasionally are increased. Escaped ventricular beats were seen both during right and left ocular pressure.

7. Pain, flushing of the face, and apnea during ocular pressure, are much less pronounced in tabetics than in non-tabetics.

8. The effects on the rate and on the rhythm of the heart produced by ocular pressures are not constant, differing in different individuals and in the same individual from time to time. The duration and the degree of pressure play an important part in the degree of inhibition.

I am greatly indebted to Dr. A. E. Cohn for his help and guidance throughout this investigation. I wish to express my thanks to Dr. Henry A. Christian for making this work possible.

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# COARSE AURICULAR FIBRILLATION IN MAN*

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Faradic stimulation of the auricles of animals may produce any one or any combination of the following closely related conditions:

1. *Fine Fibrillation.*—This may be produced by auricular stimulation alone, but it is favored by simultaneous stimulation of the right vagus nerve.[1] During fine fibrillation the auricles appear dilated and motionless and from the mechanical point of view they may be said to be paralyzed. Close inspection, however, shows that they are the seat of numerous incoordinated contractions involving very small muscle bundles. It seems certain that this fine type of fibrillation produces no auricular venous waves of any magnitude.[2] On the other hand, changes in the electrical potential of different portions of the auricular musculature may cause distinct movements of the galvanometer string. The ventricles, being stimulated irregularly, take on a disorderly rhythm.

2. *Coarse Fibrillation.*—No sharp line separates this from the previous type and one may therefore speak of auricular fibrillation as being more or less coarse. When quite coarse the auricles can be seen to execute a series of very rapid, irregular contractions, which can be recorded by the myocardiograph.[3] These contractions differ from normal auricular systoles in that they are incoordinated. The entire auricle does not take part in each contraction, and at times wave-like peristaltic movements of the muscle may be seen. These auricular activities produce movements of the galvanometer string which are similar to, though usually coarser than those produced by the fine type of fibrillation. According to the experiments of Rothberger and Winterberg,[4] and of Lewis,[5] however, coarse electrical changes are not

* Submitted for publication Dec. 7, 1914.

* From Department of Internal Medicine, University of Michigan.

1. Robinson, G. C.: The Influence of the Vagus Nerves on the Faradized Auricles in the Dog's Heart, Jour. Exper. Med., 1913, xvii, 429.

2. Rihl, J.: Ueber das Verhalten des Venenpulses bei Flimmern der Vorhöfe des Säugethierherens mit Rücksicht auf den Venenpulses beim Pulsus irregularis perpetuus, Ztschr. f. exper. Path. u. Therap., 1910, vii, 693.

3. Winterberg, H.: Ueber die Wirkung des Nervus vagus und accelerans auf das Flimmern des Herzens, Arch. f. d. ges. Physiol., 1907, cxvii, 223.

4. Rothberger, C. J., and Winterberg, H.: Ueber das Electrokardiogramm bei Flimmern der Vorhöfe, Arch. f. d. ges. Physiol., 1910, cxxxi, 387.

5. Lewis, T.: Auricular Fibrillation and Its Relationship to Clinical Irregularities of the Heart, Heart, 1909-1910, i, 306.

necessarily associated with coarse mechanical movements. As in the fine type of auricular fibrillation, the ventricles are stimulated irregularly and consequently take on a disorderly rhythm. The effect of such coarse auricular fibrillatory movements on the venous pulse seems variable. In Lewis' experiments the ventricular systoles caused the principal waves on the venous pulse. On the other hand, it seems probable from inspection of the auricular movements, from myocardiograph tracings, and from certain observations on the venous pulse,[6] that the auricular movements of coarse fibrillation may at times influence the venous pulse to a noteworthy degree.

3. *Auricular Tachysystole.*[7]—Rapid coordinated contractions of the auricles may occur as a result of faradic stimulation; particularly when, as in Robinson's experiments, the faradic stimulus is relatively weak and the electrodes are closely approximated. Auricular tachysystole is favored by simultaneous stimulation of the left vagus nerve. In Robinson's experiments the rapid auricular contractions were in most cases associated with fine fibrillatory movements of at least a portion of the muscle.

Observations on man have shown that these various types of irregularity produced by faradic stimulation of the auricles find their counterparts in clinical irregularities. Auricular tachysystole is characterized by an extremely rapid auricular rate (200 to 370 per minute).[8] Auricular waves are present on the jugular pulse and the ventricles usually respond to every second, third or fourth auricular beat. The string galvanometer shows a characteristic though abnormal deviation for each auricular systole, indicating that all have arisen from a definite region of the auricular muscle. The galvanometer records from man differ in this respect from those obtained by Robinson when auricular tachysystole was produced by faradization; for in the latter condition the deviations of the galvanometer string were much more irregular, possibly on account of the associated fibrillation. In man the intimate

6. Hewlett, A. W.: Auricular Fibrillation Associated with Auricular Extrasystoles, Heart, 1910, ii, 107.

7. In this article we have avoided the term "auricular flutter" because it seems to have been used to designate two separate conditions. Auricular flutter, as described by clinicians, is a condition in which very rapid, regular and coordinated auricular systoles arise from an abnormal but fixed region of the auricular muscle. This condition is called auricular tachysystole in the present article. Physiologists have used the term "flutter" to designate any coarse fluttering movements of the auricles. Some of these are manifestly closely related to fibrillation. In that sense the case here reported might be regarded as flutter; but we have preferred the term "coarse fibrillation," in order to emphasize the separation from clinical "flutter."

8. Ritchie, W. T.: Further Observations on Auricular Flutter, Quart. Jour. Med., 1913, vii, 1.

relationship between tachysystole and fibrillation is shown, however, by the frequent passage of the one into the other.[8, 9]

Auricular fibrillation as observed in man usually causes rapid movements of the galvanometer string (400 to 500 or more per minute). In some patients these movements are distinctly coarser than in others. As has been pointed out, however, definite conclusions as to the coarseness of the mechanical movements of the auricles cannot be safely drawn from galvanometer records. Auricular fibrillation in man is almost invariably associated with a venous pulse of the ventricular type. Even during the long pauses that may intervene between ventricular systoles, there is rarely evidence of auricular activity. Only occasionally have small waves been encountered which may reasonably be attributed to the fibrillations;[5, 10, 11] but so far as we have been able to determine, these have always been insignificant when compared with the waves produced by the ventricular contractions. The following case is reported because the venous tracing was dominated by waves which were caused, as we believe, by an unusually coarse type of auricular fibrillation.

## CASE REPORT

*History.*—J. K., a farmer, aged 47, entered the University Hospital April 22, 1914, complaining of shortness of breath. His family and personal history were unimportant. His present trouble began about six months before entering the hospital with dyspnea on exertion, which had persisted up to admission. He had also suffered from some precordial distress, both palpitation and pain. He had some cough and sputum, but had never had edema.

*Physical Examination.*—The patient was a well-nourished but slightly cyanotic man. The thorax was of the emphysematous type. It was hyperresonant on percussion, and a few crackles were heard at the bases. The cardiac impulse was diffuse, but most prominent in the fourth intercostal space in the mammary line. Although no marked change in cardiac dulness could be made out on percussion, the orthodiagraph showed a moderate enlargement of the heart shadow (142 sq. cm.). The heart action was very irregular. The sounds at the apex were clear, except for a slight systolic murmur after the longer diastolic pauses. The second sound was reduplicated over the pulmonic area. There was no edema and no enlargement of the liver. The larger pulse-beats came through the pressure cuff at a pressure of 150 mm. of mercury. The blood and urine were negative.

During his stay of ten days in the hospital the patient was treated with tincture of digitalis and the heart rate became considerably slower. Simultaneous venous and electrocardiographic records were taken on April 10, before admission to the hospital, and on April 24 and 30.

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9. Robinson, G. C.: The Relation of Auricular Activity Following Faradization of the Dog's Auricle to Abnormal Auricular Activity in Man, Jour. Exper. Med., 1913, xviii, 704.

10. MacKenzie, J.: The Interpretation of the Pulsations in the Jugular Veins, Am. Jour. Med. Sc., 1907, cxxxiv, 12.

11. Wenkebach, K. F.: Beiträge zur Kenntnis der menschlichen Herztätigkeit, Arch. f. Anat. u. Physiol. Physiol. Abth., 1907, i.

THE GRAPHIC RECORDS

The electrocardiograms obtained differed in no essential particular from those frequently obtained from patients showing auricular fibrillation. The ventricular contractions, which occurred at irregular intervals, showed, as a rule, normal ventricular complexes which were interrupted here and there by abnormal complexes due to ectopic beats of ventricular origin. Normal P waves were absent, but throughout the tracings rather coarse vibrations of the string during diastole, such as occur in certain cases of auricular fibrillation, were present. These became particularly evident during the longer diastolic pauses of the slow heart-rate that developed during his stay in the hospital. These undulations occurred at the rate of about 450 per minute.

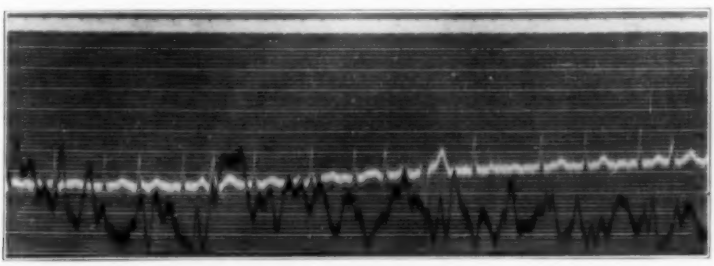

Fig. 1.—Electrocardiogram and venous pulse. Lead II (right arm and left leg). Sensitivity, 10 mm. equals 1 millivolt. Taken April 10, 1914, before treatment was begun. The ventricles are absolutely irregular. A single ectopic beat of ventricular origin occurs. The venous waves cannot be definitely correlated with the ventricular systoles.

Particular interest is attached to the venous tracings. Instead of a well-defined positive ventricular pulse, such as is commonly seen in auricular fibrillation, the venous waves occurred irregularly and were not readily correlated with the ventricular systoles. During the more rapid ventricular rate present in the earlier tracings the venous records were not readily analyzed (Fig. 1). When records were obtained during the slower heart action, however, it become evident that many of the venous waves which occurred during the latter portions of the long diastolic pauses could not possibly have been dependent on the contractions of the ventricles (Figs. 2, 3 and 4). They were neither stasis waves nor the *h* waves of Hirschfelder. They must have been due, therefore, to the activity of the auricles. We found, furthermore, that many of the unusually large waves during ventricular systole bore no definite or constant time relation to the systole itself (Figs. 2, 3 and 4). In our opinion, these waves were produced by auricular con-

tractions which occurred while the tricuspid valves were closed, being similar to the unusually high venous waves produced whenever auricles and ventricles contract simultaneously.

### THE INTERPRETATION OF THE RECORDS

Since most of the prominent waves on our venous tracings were, as we believe, due to auricular activity, the question arises whether or not our case should be classed as one of auricular tachysystole. It resembled this condition in so far as rapid auricular contractions were recorded in the venous tracings. On the other hand, it differed in the following particulars: 1. The auricular contractions were not regular. 2. There was no constantly recurring auricular complex on the electrocardiogram. 3. No definite relation existed between the waves on the electrocardiogram and those on the venous pulse. At times the venous pulse showed marked waves while the galvanometer string was comparatively motionless (Fig. 3). Furthermore, although the movements of the string and the venous waves had approximately the same rate of vibration, there was no definite time relationship between the two. The onsets or crests of the one set of waves bore no definite relation to the onsets or crests of the other. It seems evident, therefore, that we are not dealing, as in auricular tachysystole, with a series of rapid coordinated auricular contractions all of which arose from the same region of the heart, but with a series of irregular contractions of the auricles which, from their lack of relationship to the galvanometer curves, were apparently originating at different points and

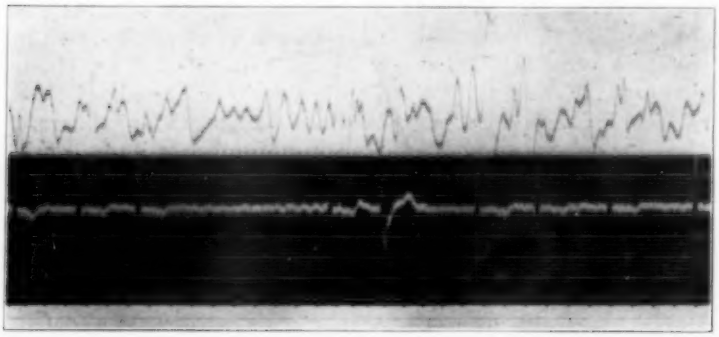

Fig. 2.—Electrocardiogram and venous pulse. Lead I (right arm and left arm). Sensitivity, 10 mm. equals 1 millivolt. Taken April 30, 1914, after treatment with rest and digitalis. The ventricles are absolutely irregular but beating at a slow rate with some very long diastolic pauses. The venous curve shows prominent waves during the long diastolic pauses.

progressing in different directions over the auricular musculature. The separation from tachysystole is also favored by the fact that the ventricular rhythm was absolutely irregular and that digitalis slowed the heart and atropin quickened it, not by sudden jumps from one rate to another, but by gradual changes in rate analogous to those produced when these drugs are given to patients suffering from the ordinary type of auricular fibrillation.

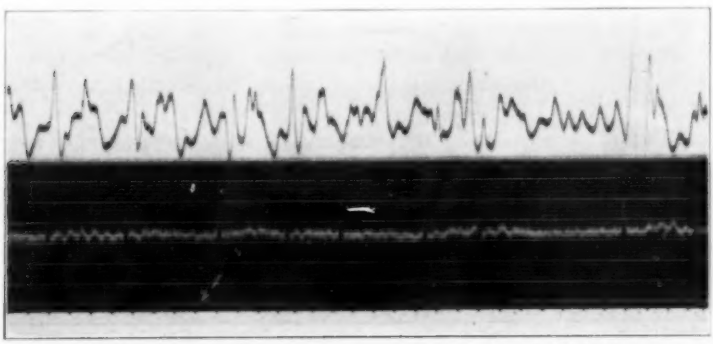

Fig. 3.—The electrocardiogram and venous pulse. Lead II (right arm and left leg). Sensitivity, 10 mm. equals 1 millivolt. Taken shortly after Figure 2, shows the same characteristics except that R is shorter, and coarser electrical waves are seen during certain diastoles. The venous waves during the systoles bear no definite time relationship to the electrical complexes.

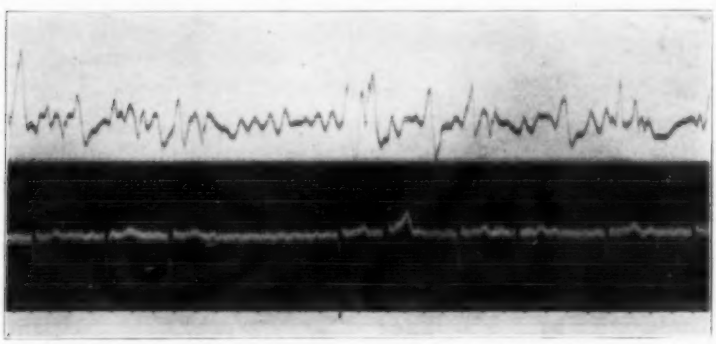

Fig. 4.—Electrocardiogram and venous pulse. Lead III (left arm and left leg). Sensitivity, 10 mm. equals 1 millivolt. Taken shortly after Figure 3; shows the same characteristics, except that the most prominent wave of the ventricular complex is in the opposite direction.

It seems to us, therefore, that both by exclusion and by direct analogy with animal experiments our tracings are best explained by assuming that the auricles were fibrillating in such a coarse manner that they produced marked venous waves. This hypothesis explains

the rapid auricular rate. The lack of correspondence between venous and galvanometer records is explained by the fact that in fibrillation the mechanical movements of the auricles and the differences in potential between two given portions of the auricular muscle are more or less dissociated on account of the local character of the contractions and the interference phenomena produced by the simultaneous occurrence of more than one partial contraction. The effects produced by digitalis and by atropin were those usually produced by these drugs during the ordinary type of auricular fibrillation.

A word should be said about the method of recording the venous pulse, and its possible relation to our records. In making venous records we used the usual receiving tambour and air transmission. A small mirror was pasted on the recording tambour and a beam of light projected from this mirror was photographed on the moving sensitized surface. The inherent vibration of the system was 25 to 40 per second, a rate much faster than that of the mechanical recorders commonly used for the venous pulse, and sufficiently fast for the accurate reproduction of all but the most sudden venous waves. It might be questioned whether, with this more accurate recorder, mechanical evidence of auricular fibrillation might not be more frequently obtained than is usual on venous records. We suspect that this may be the case, but in a limited experience with the method we have found that venous tracings from the other cases of auricular fibrillation examined showed no such prominent waves as in the case here reported. The waves cannot, therefore, be attributed to the method used, but are due to peculiarities in the activity of the auricles.

## CONCLUSIONS

1. A case of continuous irregularity is reported in which the venous curves were characterized by numerous very rapid and irregular waves produced by auricular activity. These waves bore no definite relationship to the auricular fluctuations of the galvanometer string.

2. We believe the condition to be one of unusually coarse auricular fibrillation.

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# CLINICAL CALORIMETRY

FIRST PAPER

## A RESPIRATION CALORIMETER FOR THE STUDY OF DISEASE*

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### HISTORICAL

A respiration calorimeter is an apparatus designed for the measurement of the gaseous exchange between a living organism and the atmosphere which surrounds it, and the simultaneous measurement of the quantity of heat produced by that organism.

The first contrivance of this nature was described by Lavoisier in 1780. It will be remembered that Lavoisier was the first to comprehend the significance of the then newly discovered oxygen. Primitive though the apparatus, yet intellectually inspiring was the mind which so early grasped the principles and understood many of the difficulties.

Apparatus for the measurement of the respiratory exchange was perfected before that for the measurement of heat production. Thus, Regnault and Rieset[1] in 1850 designed an air-tight apparatus in which an animal was placed; the carbonic acid formed in it was removed by pumping the air into flasks filled with potash, and oxygen was added from time to time as it was required. This is the *closed circuit* system which in a modified form is used to-day.

The historic respiration apparatus of Pettenkofer[2] and Voit was completed in 1862. This machine was capable of measuring the carbon dioxid output of a man within 1 per cent. of error. As early as 1866 Voit began computing from the substances oxidized in the body the quantity of heat which should have arisen from the destruction of those substances. This method is known as *indirect calorimetry*.

* Submitted for publication Oct. 20, 1914.

* From the Russell Sage Institute of Pathology, in affiliation with the Second Medical Division of Bellevue Hospital.

1. Regnault and Rieset: Ann. d. Chem. u. Pharmakol., 1850, lxxiii, 92, 129, 257.

2. Pettenkofer: Ann. d. Chem. u. Pharmakol. Supplement 2, 1862.

In 1885, Rubner, working in Voit's laboratory, published results concerning the calorimetry of foods. Accurate determinations of the heat value of urea, and of dry urinary solids were made for the first time. This work established biological standards for the heat values of proteins, carbohydrates and fats which are to-day accepted.

About the same time a calorimeter for the measurement of the heat production in man was set up in Voit's laboratory and many experiments were made with it by Carl Voit and his brother Erwin Voit. The results were apparently not satisfactory, for nothing was ever published on the subject. At this time Atwater was in Voit's laboratory, and in 1888 published from that laboratory an article on the absorption of the flesh of fish.

Atwater's interest in nutrition had already been stimulated by Johnson and Brewer at Yale, and through studies in agricultural and physiological chemistry in Berlin in 1869-71. In 1877 he began investigations into dietary requirements of the people. It was Atwater's association with Voit and with Rubner, however, which gave him his knowledge of the principles of the subject of calorimetry as applied to the living organism. These facts, which are not widely known, emphasize again the overwhelming debt which American science owes to Germany.

In 1894 Rubner built the first successful respiration calorimeter. He built it largely with his own hands and with the very moderate means available in his laboratory at Marburg where he had become professor of hygiene. Voit, on hearing the news, said that it was the most important invention of its kind since the invention of the thermometer. Rubner's calorimeter, which measured the heat production of a dog, was associated with the mechanism of a Pettenkofer respiration apparatus which determined the carbonic acid output of the animal. Thus *indirect calorimetry* could be compared with *direct calorimetry*. For example, if the nitrogen in the urine and feces of a dog fed with meat and fat were determined, and this nitrogen were multiplied by 6.25, the quantity of protein destroyed could be estimated. Since each gram of protein yields 4.1 calories of heat in the body, the quantity of heat produced from protein would be

$$\text{Grams excreted } N \times 6.25 \times 4.1$$

To estimate the quantity of fat oxidized the quantity of carbon contained in the protein destroyed (which amounts to grams excreted $N \times 3.28$) was deducted from the quantity of carbon contained in the

3. For the history of animal calorimetry see Rubner: Tigerstedt's Handbuch der physiol. Methodik. i, 150; Johansson, Abderhalden's Handbuch der biochem. Arbeitsmethoden, Berlin, 1910, iii, 1114.

excreta, that is, the sum of that in the urine, feces and respiration. The remainder represented the quantity of expired carbon derived from the oxidation of fat. Since fat contains 76.5 per cent. of carbon and 1 gm. of fat yields 9.3 calories, it was easy to calculate the heat production derived from fat. Recapitulating, one may express the heat produced from fat in the formula:

$$\text{Total C} - (\text{N} \times 3.28) \text{ divided by } 76.5 \times 100 \times 9.3$$

Adding together the heat calculated as that which should have arisen from the protein and fat metabolized, Rubner found that this sum was exactly the amount of heat given off by the animal as measured by the calorimeter. This was the first long-sought demonstration of the law of the conservation of energy applied to animal life.

After returning to America, Atwater in 1892 began work on a calorimeter which could measure the heat production in man. In 1894 the United States government began to appropriate funds for investigations into the nutrition of the people and placed the distribution of these funds in the hands of Professor Atwater. A portion was wisely used in the construction of the Atwater-Rosa[4] respiration calorimeter, the earlier description of which appeared in 1897. In 1893 C. F. Langworthy and in 1895 F. G. Benedict became associated with the undertaking. Shortly after the completion of the apparatus, Rosa, the expert physicist, to whose skill its successful completion was largely indebted, retired from direct association with the enterprise, although, as professor of physics at Wesleyan he was still frequently consulted until, in 1901, he became chief physicist of the Bureau of Standards at Washington. The Atwater-Rosa calorimeter demonstrated that direct and indirect calorimetry agreed in man, not only during rest, but also during periods when mechanical work was performed.

The original Atwater-Rosa calorimeter was associated with a respiration apparatus of the type designed by Pettenkofer, which measured only the carbon dioxid output. Calculated on this basis the production of heat might show a maximum error of 24 per cent., depending on whether carbohydrate or fat was being oxidized. At a later date funds were granted to Atwater by the Carnegie Institution in order to apply the principle of the closed circuit of Regnault and Rieset to the apparatus so that the oxygen absorption might also be determined. The modification of the apparatus along these lines was begun in 1902, and the work accomplished during 1903 to 1905 was done during a period when Atwater was in full control of the undertaking. Atwater's illness

4. Atwater and Rosa: Report of the Storrs Agric. Exper. Station, 1897, p. 212.

began in 1905, his retirement took place in 1906 and he died in 1907.

With the improved apparatus, publication[5] concerning which fell in 1905, not only heat production and carbon dioxid output were accurately measured, but the absorption of oxygen as well. It thus became possible to measure not only the non-protein carbon in the respiration, but also to calculate how much of the oxygen absorbed was devoted to the destruction of non-protein material; that is to say, fat and carbohydrate. The value of this knowledge becomes apparent when it is realized that one liter of oxygen used for the oxidation of fat yields 4.686 calories, whereas when the same volume is used to oxidize starch 5.047 calories are set free, a difference of over 7 per cent. When carbohydrate is oxidized the volume of oxygen absorbed is equal to the volume of carbon dioxid expired and the *respiratory quotient* equals unity.

$$\text{R. Q. equals } \frac{\text{Vol. } CO_2}{\text{Vol. } O_2} = 1$$

When fat is oxidized, however, the respiratory quotient is only 0.70. Respiratory quotients (corrected from protein influence) which run intermediate between 0.70 and 1.00 are deemed to represent the oxidation of mixtures of carbohydrates and fats, and the heat value of a liter of oxygen varies accordingly. Thus a quotient of 0.85 represents the oxidation of fat and carbohydrate together in such a proportion that 49 per cent. of the calories produced are derived from carbohydrate and 51 per cent. from fat. Under these circumstances, 1 liter of absorbed oxygen represents 4.863 calories liberated in the organism. Tables giving these data were first published by Zuntz.[6]

The ability to determine the oxygen absorption with exactness abolished a possible error of considerable magnitude in the calculations of indirect calorimetry. This improvement brought the apparatus to a high degree of perfection. The Carnegie Institution of Washington has richly provided for the higher development of the work in the Nutrition Laboratory at Boston, which represents the realization of Atwater's ambition for the establishment of a separate laboratory for this work. Dr. Benedict is here the controlling genius, while the original Wesleyan calorimeter, now removed to Washington, is under the direction of Dr. C. F. Langworthy.

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5. Atwater and Benedict: Carnegie Institution of Washington, 1905, Pub. 42. See also, Benedict and Carpenter: 1910, Pub. 123.

6. Zuntz and Schumburg: Studien zu einer Physiologie des Marches, Berlin, 1901. See also, Williams, Riche and Lusk (Jour. Biol. Chem., 1912, xii, 357), for other references.

## ANIMAL CALORIMETRY AT THE CORNELL UNIVERSITY MEDICAL COLLEGE

At the time of my appointment to the professorship of physiology at the Cornell University Medical College, the authorities liberally provided for the construction of a respiration apparatus. Dr. Murlin spent a part of the summer with Dr. Benedict in Boston, where he freely received every privilege of the laboratory. After considerable discussion, I decided to have a calorimeter constructed which was small enough for use with dogs and babies, work which, up to that time, had not been included in the program of the Boston laboratory. The construction of this apparatus was entrusted to the capable management of Dr. H. B. Williams.[7] Full and grateful acknowledgment is due to Dr. F. G. Benedict, who has ever given all that counsel which his unique experience in calorimeter construction makes of highest value.

The problem of the measurement of 7 calories of heat produced in an hour by a baby weighing 3 kg. was different from that presented by the measurement of 70 calories produced by an adult. This led to the addition to the calorimeter of certain refinements in technical construction which are due to Dr. Williams. The small calorimeter has been successfully used in many experiments on dogs and babies. For the first time direct and indirect calorimetry were found to agree during hourly periods of experimentation.

The method employed with dogs was to determine the *basal metabolism* as measured by that quantity of heat which was produced by the resting animal when there was no food in the gastro-intestinal tract, and to compare this metabolism with that found at times following the ingestion of various foods. It was found that three or four hours of observation sufficed to indicate the influence of ingested food.

The satisfactory working of the apparatus used in accordance with these principles encouraged me to believe that valuable results might be obtained concerning the nutrition of patients if a similar, though larger, apparatus were placed in Bellevue Hospital. Before embarking on the undertaking, inquiry was made of Dr. Benedict if he did not desire to investigate this field by establishing a calorimeter in the Peter Bent Brigham Hospital in Boston. As the reply was in the negative, it appeared justifiable to seek money and opportunity for the accomplishment of this work.

Sufficient funds were obtained from the Russell Sage Institute of Pathology for a period of five years. The former arrangement between this institute and the City Hospital had just been terminated. A new arrangement was entered into with the trustees of Bellevue Hospital

7. Williams: Jour. Biol. Chem., 1912, xii, 317.

which enabled the institute to construct the first respiration calorimeter ever established in a hospital. Dr. Eugene F. Du Bois was appointed medical director, and the whole undertaking has enjoyed the faithful service of chemists, mechanics and nurses who have contributed to its success. A factor of especial encouragement has been the personal interest in the undertaking manifested by the visiting physicians, Drs. W. Gilman Thompson, C. L. Dana and Warren Coleman. The last-named has taken part in the actual work of the institute.

It is also a pleasure to acknowledge with thanks many helpful suggestions made by Drs. Langworthy and Milner of Washington.

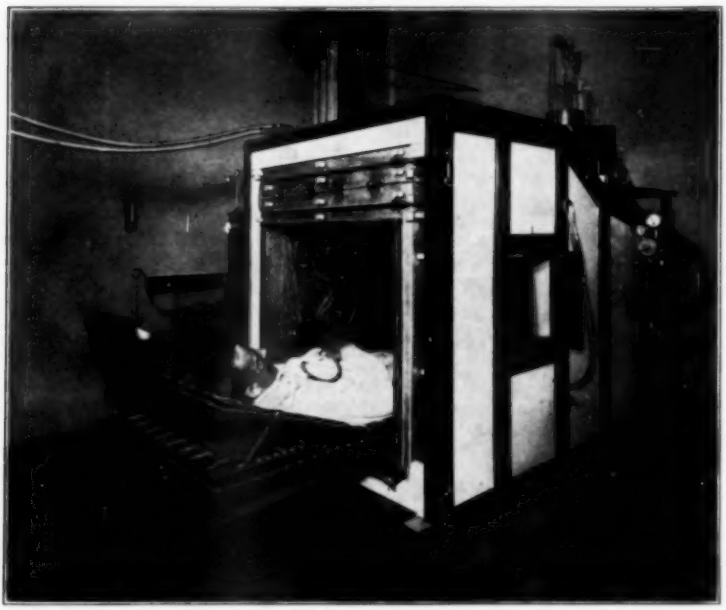

Fig. 1.—Respiration calorimeter with the patient half-way in. On his chest can be seen the tube of the Bowles stethoscope strapped over the heart. Coiled up on the wall is the rectal thermometer not yet inserted. Just below this is one of the units of the air thermometer and to the right is the telephone.

An Atwater-Rosa-Benedict respiration calorimeter, together with the instruments of precision applied to it by Williams, and certain new modifications which were the result of advice and experience, was established in Bellevue Hospital. The papers which follow are descriptive of the calorimeter (Fig. 1) and the results obtained with it. The patient lies quietly for three or four hours on a comfortable bed in the chamber of the apparatus, breathing the purest air, without the possi-

bility of harm. The long periods of the older respiration chambers and the nose- or mouth-pieces of the short-period apparatus are not disturbing factors. For the benefit of those who are interested in the work and who do not care to follow the details of the technical description of the apparatus, the following summary will suffice.

## PRINCIPLE OF THE ATWATER-ROSA-BENEDICT RESPIRATION CALORIMETER

The apparatus is divided into two functional parts, one for measuring the gaseous exchange, the other for measuring the heat production of the subject. A schematic presentation is here given (Fig. 2).

*The Gas Analysis.*—The inner lining of the apparatus presents an air tight copper box having a capacity of 1,123 liters. One end of the box, through which the patient lying on the bed is admitted, may be closed with a glass plate by means of wax. The air within the box is purified by drawing it out of an opening in the box through a rubber tube and forcing it by means of a rotary blower through a system of *absorbers*, whence it returns again to the box by another rubber tube. It passes (see diagram) first through sulphuric acid (1), which removes the water, then through moist soda lime (2), which removes the carbon dioxid, and next through sulphuric acid (3), which absorbs the moisture taken from the soda lime. If the bottles be previously weighed, the gain in weight of 1 represents water absorbed, and the gain in weight of 2 plus 3 equals the carbon dioxid absorbed. By this method the water and carbon dioxid produced by a man are taken from the air, while oxygen within the chamber is being absorbed by the man himself. This causes a diminution in the volume of the contents of the box. In order to replace the oxygen used, oxygen is automatically fed into the system from an oxygen cylinder which may be weighed before and after the period. The automatic feeding of oxygen into the box is accomplished by means of a spirometer whose interior is connected with the interior of the calorimeter chamber. As the volume of the air in the box decreases, the spirometer falls until a certain point is reached, at which an electric contact releases a clamp, which allows oxygen from the oxygen cylinder to enter the box, causing the spirometer to rise, break its electric contact and clamp off the oxygen supply. So sensitive is the spirometer to the movement of the patient that a device called a "work adder" has been attached to it, which records the subject's movements.

At the beginning of an hourly period of experimentation an observer at the table calls "time." At this instant the rotary blower is stopped, the air current switched so as to pass through a new set of weighed absorbers and then the rotary blower is started again. At the word "time" an operator also turns a pet-cock which cuts off the respiratory chamber from the spirometer cylinder, which is then filled, always to a given point, with oxygen from the oxygen cylinder. The pet-cock is now opened and a freshly weighed oxygen cylinder is placed in the position of the other, which is removed. Repeating these procedures an hour later, one may determine by difference in weight the gain of water and carbon dioxid by the absorbers and the loss of oxygen by the cylinder. The figures are subject to corrections due to (1) gain or loss of water or carbon dioxid content in the box itself, during the period, which gain or loss must be added to or subtracted from the increase in weight of the absorber system. This gain or loss of water and carbon dioxid in the box also affects the volume of the air in the box and, therefore, the quantity of oxygen admitted, as do, in addition (2), a change in temperature within the box and (3) a change in barometric pressure. These corrections must be made in order to determine whether oxygen is to be added or subtracted from the quantity which has been furnished from the oxygen cylinder. The result

gives the quantity of oxygen which the man has absorbed. It is apparent that all the errors of determination fall on the oxygen, and yet the exactness of the method is witnessed by the close approximation in alcohol check experiments of the theoretical and actual values for oxygen consumed.

If a person in the calorimeter moves even the arm during the critical moments just before "time" is called, the increased local heating of the air may cause the spirometer to rise to a considerable height, of which the air

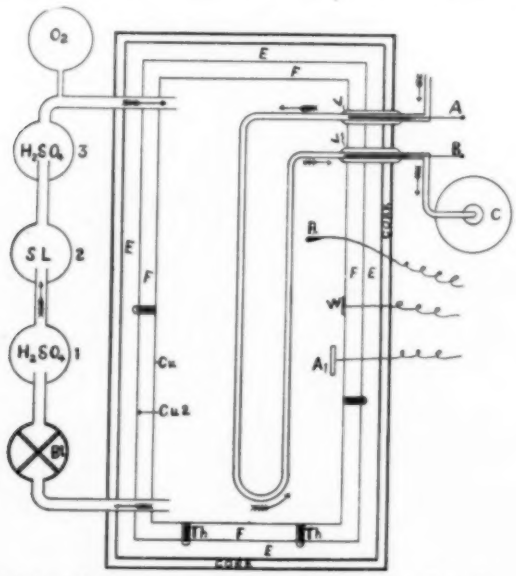


Fig. 2.—Schematic diagram of the Atwater-Rosa-Benedict respiration calorimeter.

Ventilating System:
- $O_2$, Oxygen introduced as consumed by subject.
- 3, $H_2SO_4$ to catch moisture given off by soda lime.
- 2. Soda lime to remove $CO_2$.
- 1, $H_2SO_4$ to remove moisture given off by patient.
- Bl., Blower to keep air in circulation.

Indirect Calorimetry:
- Increase in weight of $H_2SO_4$ (1) = water elimination of subject.
- Increase in weight of soda lime (2) + increase in weight of $H_2SO_4$ (3) = $CO_2$ elimination.
- Decrease in weight of oxygen tank = oxygen consumption of subject.

Heat-Absorbing System:
- A, Thermometer to record temperature of ingoing water.
- B, Thermometer to record temperature of outgoing water.
- V, Vacuum jacket.
- C, Tank for weighing water which has passed through calorimeter each hour.
- W, Thermometer for measuring temperature of wall.
- A1, Thermometer for measuring temperature of the air.
- R, Rectal thermometer for measuring temperature of subject.

Direct Calorimetry:
- Average difference of A and B × liters of water + (gm. water eliminated × 0.586) ± (change in temperature of wall × hydrothermal equivalent of box) ± (change of temperature of body × hydrothermal equivalent of body) = total calories produced.

*Th*, thermocouple; *Cu*, inner copper wall; *Cu*$_2$, outer copper wall; *E*, *F*, dead air spaces.

thermometers inside the box fail to make compensatory record, and the oxygen determination will be too low in that hour and too high in the next.

Analysis of the air in the interior of the chamber is made just before the beginning of each hour by passing ten liters of air from the box through three U-tubes containing, respectively, sulphuric acid, soda lime and sulphuric acid, then through a Bohr gas meter and back into the box again. This is called the "residual analysis."

Under the conditions present in the respiration apparatus, carbon dioxid is measured with the greatest ease and accuracy. Oxygen is also measured with accuracy if the person within the box lies perfectly quietly for ten minutes before the end of the period, whereas water production is the least accurate of all the determinations, on account of the varying hygroscopic condition of the walls, bedding and other surfaces within the closed spaces of the apparatus.

*The Measurement of Heat Produced.* — Roughly speaking, one-quarter of the heat eliminated by a man is present in the water vapor which is absorbed by the first sulphuric acid bottle on the absorber table. At 20 degrees C. 0.586 calories are contained as latent heat in 1 gm. of vaporized water.

The rest of the heat loss takes place by radiation and conduction. It is this heat which is measured by the calorimeter, itself. The mechanism of the calorimeter is essentially two-fold. In the first place, there is no heat loss through the walls of the apparatus, and, secondly, the heat produced by a man within is removed from the chamber by a current of cold water flowing through copper tubes suspended from the upper wall of the chamber. If the walls allowed no heat to pass, it is obvious that without the cooling effect of the water-pipes the temperature of the air in the box would soon attain the temperature of the human body instead of being about 23 C., at which it is usually held. The apparatus is therefore a constant-temperature, water-cooled calorimeter. It is evident that if no heat is allowed to pass through the walls of the calorimeter, then the heat produced within the chamber will be removed in the current of cold water flowing through the heat-absorbing pipes inside the chamber of the apparatus. If the temperatures of the ingoing and of the outgoing water are known and the quantity of water which has passed through the heat-absorber during an hour is measured, the quantity of heat carried away in the current of water can be accurately determined. For example, if the difference between the temperature of the ingoing and outgoing water is 2.50 degrees, and 20 liters of water have passed through the heat absorber in one hour, then 50 calories of heat have been carried away from the apparatus during the period. If the temperature of the walls within the apparatus has undergone a change this value is subject to corrections, but otherwise the total heat elimination of the person is meas-

ured by the 50 calories so determined plus the heat value of water vaporized during the hour.

To obtain an even flow of water through the heat-absorber the water is supplied from a constant-level tank placed above the calorimeter. To obtain ingoing water of an even temperature, Williams passed the previously ice-cooled water current through a Gouy temperature regulator and then through a current regulator designed by himself. These improvements allow the ingoing water to enter the calorimeter at a temperature which may not vary more than 0.02 C. during hours of experimentation and, for the first time, permitted the exact measurement of small quantities of heat in this type of apparatus. The temperatures of the ingoing and outgoing water are taken every four minutes by electrical resistance thermometers and are read in connection with a galvanometer and Kohlrausch bridge on an observer's table. The quantity of the water-flow is determined by weighing; the water is diverted at the call of "time," so that the exact quantity for the hour is collected in a previously weighed receptacle.

Having learned how the heat produced within the apparatus is carried away, the problem of how to prevent loss of heat through the walls of the chamber remains to be discussed. This was accomplished through a device introduced by Rosa. The calorimeter is constructed of three walls, an inner copper wall which has already been described as the lining of the respiration chamber, an outer copper wall separated from the inner wall by a space of dead air, and an insulating wall (made of two layers of "compo-board," the space between them being filled with cork), which insulating wall is separated from the outer copper wall by a second space containing dead air. It is obvious that if the inner and outer copper walls of the calorimeter have the same temperature there will be no exchange of heat between them. Therefore, to prevent a gain or loss of heat by the inner wall, it is necessary to maintain the outer wall always at exactly the same temperature as the inner wall, under which circumstances the latter cannot gain or lose heat to its neighbor.

In order to detect differences in temperature between the outer and inner walls Rosa arranged thermo-couples in series between the two walls. In this fashion the top, sides and bottom of the box are successively tested every four minutes by an operator at the observer's table to determine whether there is any difference in temperature between the outer and inner walls. If the outer wall is found to have a different temperature from the inner wall, its temperature is brought to that of the inner wall by the following device. A cooling current of water runs through pipes between the insulating and outer copper wall, and in this same space, along the line of the pipes, run "Therlo" resistance

wires carrying an electric current for the warming of this interspace (Fig. 1). By varying the intensity of the electric currents which severally supply the spaces to top, sides and bottom, the temperature of these spaces can be so controlled as to heat or cool the outer copper wall and maintain it at exactly the same temperature as the inner copper wall. This is the effective system which prevents a loss or gain of heat through the wall of the calorimeter.

Resistance thermometers are attached to the inner walls of the calorimeter, and if the temperature of the walls rises or falls between the beginning and end of the experiment, a correction must be made. It has been found that 19 calories are absorbed by the Sage calorimeter when the inner wall rises 1 degree. Conversely, 19 calories are given up by a fall of 1 degree. This is the *hydrothermal equivalent* of the box.

SCHEME OF EMPLOYMENT OF OBSERVERS IN A CALORIMETER EXPERIMENT

| Period of Observation | Observer 1, at Electrical Control Table | Observer 2, in Charge of Experiment | Observer 3, Calculator |
|---|---|---|---|
| Eight minutes before | Brings wall into exact thermal equilibrium | Signals subject to lie absolutely quiet. | Starts passing first 10 L. sample of residual air through U tubes. |
| Five minutes before | ..... | Starts kymograph record of movements of spirometer | ..... |
| Four minutes before | ..... | ..... | Finishes first and starts second residual |
| One-half minute before | Takes final reading of air, wall and rectal temperature | Sets barometer | Finishes second residual |
| At "Time" | Presses button which diverts stream of water from weighing tank | Shuts spirometer off from box. Fills to standard level from oxygen tank. | Stops ventilating current of air. Turns valve to pass air through newly weighed absorbers. Starts ventilating current. |
| Immediately after "Time" | Starts taking readings every four minutes of ingoing and outgoing water, of air, walls, rectal and surface thermometers. Reads and adjusts temperature of top, sides and bottom of calorimeter, of the ingoing air and water every four minutes, or oftener if necessary. | Records and sets work-adder. Signals to subject that he may move. Weighs oxygen tank and connects with box again. Weighs sulphuric and soda lime bottles. Connects them up again and tests for leaks. During remainder of hour counts pulse, inspects valves for leaks, adjusts temperature of room, watches subject, etc. | Weighs water tank which has received all the water from the heat absorber during the past hour. Diverts stream of water to this tank again. Records barometer. Weighs residual. Calculates results of the hour just finished. |

The temperature of the air entering the box from the absorbing table is always heated to exactly the same temperature as the air leaving the box.

Finally, an electric resistance thermometer inserted 10 or 12 cm. into the rectum of the person in the calorimeter gives information regarding the retention or loss of heat in his organism. The specific heat of a man is assumed to be 0.83, that is to say, 0.83 calory raises 1 kilogram 1 degree. If, therefore, the body temperature of a man weighing 70 kg. rises or falls 1 degree, the quantity of heat lost or

gained by the body will be 70 × 0.83 or 58.1 calories. This is on the assumption that the rise of body temperature is everywhere the same as takes place in the rectum, a supposition which, unfortunately, is not always true.

The accompanying scheme (Table 1) gives the details regarding the employment of the three individuals who conduct a calorimeter experiment.

It may be added that special care has been taken to make the appearance of the calorimeter attractive to the eye, and that the spirit of the small ward in connection with the calorimeter work has been such that the patients have considered themselves especially fortunate when chosen for the diversion offered by a morning's occupancy of the apparatus.

## CONCLUSION

The story of the Atwater-Rosa-Benedict calorimeter has been told here for the first time in brief, comprehensive, perhaps one might say semipopular language. The Williams calorimeter has shown the influence of many simple foodstuffs which were given to dogs in health and in induced disease. The Sage calorimeter reports "of the disturbances that Nature works and of her cures," without having, as concerns the sick human being, at any time, in the slightest degree, affected any patient to his disadvantage, but rather having yielded information regarding his condition which has been beneficial in his subsequent treatment.

It seems appropriate to recall the words with which Pettenkofer and Voit closed their communication regarding diabetes in the year 1867:

> Even as anatomy has been separated from physiology, so from pathological anatomy pathological physiology will arise. Only thus will we be able to obtain a more exact knowledge of the character of disease than we now possess. Able pathologists have constantly sought to open up this field. It will gratify us if this work of ours which for the first time presents a complete picture of metabolism in disease shall inspire others to devote their abilities in this direction.

# CLINICAL CALORIMETRY

SECOND PAPER

## THE RESPIRATION CALORIMETER OF THE RUSSELL SAGE INSTITUTE OF PATHOLOGY IN BELLEVUE HOSPITAL*

J. A. RICHE AND G. F. SODERSTROM
NEW YORK

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11. Determination of water elimination.
12. Adaptability of calorimeter to varying conditions.
13. Summary and conclusions.

During the short time in which the Sage calorimeter has been in operation there have been several requests for the technical details of the construction of the apparatus. It has therefore seemed advisable to publish a brief article for those interested in calorimeters. A complete description of the Atwater-Rosa-Benedict type of apparatus will be found in the monograph by Benedict and Carpenter.[1] A number of valuable improvements are added in the shorter article by Williams.[2] The earlier publications of Atwater and Rosa[3] and Atwater and Benedict[4] describe an apparatus fundamentally the same as that now employed, but for a complete understanding of the modern calorimeter it is necessary to consult the works of Benedict and Carpenter and

* Submitted for publication Oct. 20, 1914.

* From the Russell Sage Institute of Pathology, in affiliation with the Second Medical Division of Bellevue Hospital.

1. Benedict and Carpenter: Respiration Calorimeters for Studying the Respiratory Exchange and Energy Transformations of Man, Carnegie Institution of Washington, 1910, Pub. 123.

2. Williams, H. B.: Animal Calorimetry, First Paper, A Small Respiration Calorimeter, Jour. Biol. Chem., 1912, xii, 317.

3. Atwater and Rosa: Description of a New Respiration Calorimeter, U. S. Dept. Agriculture, 1899, Bull. 63.

4. Atwater and Benedict: A Respiration Calorimeter with Appliances for the Direct Determination of Oxygen, Carnegie Institution of Washington, 1905, Pub. 42.

Williams. The description by Langworthy and Milner[5] of their ingenious automatic calorimeter should also be consulted.

The Sage calorimeter resembles Benedict's bed calorimeter, but differs in a few details. On the recommendation of Dr. Langworthy and Mr. Milner of the Department of Agriculture the outside insulation was made of pressed cork and "Compo Board." The electrical resistance thermometers for the ingoing and outgoing water were also adopted on their advice. The gas wash bottles, water heating resistance and current regulator, water coil and several other improvements were copies of those used by Williams. The soda-lime bottles and spirometer resembled those described by Benedict[6] in connection with his small apparatus.

### THE CALORIMETER ROOM

The small metabolism ward to be described is situated at the southwest corner of the new medical pavilion of Bellevue Hospital. To the north of this is a hall, now converted into a diet kitchen, which leads into the calorimeter room, formerly a small ward for convalescents. The room itself (Fig. 3) is about 5 meters square and 5 meters high. On the west side, opening on a covered balcony, is a large window in front of which stand a thermostat-controlled radiator and a "Simplex" electric heater. These are enclosed in a window box in such a manner, that by means of a blower, fresh air can be drawn in through the window, driven over the heaters and out into the room. Unfortunately, the daylight is not strong and needs to be supplemented by two powerful tungsten lamps.

In the center of the room stands the calorimeter, at the side of which is the observer's platform, raised a short distance above the floor to permit the passage of the numerous water pipes and electrical conduits. On the east side of the room is the panel box where the heavy feed wires are led up from the basement. Next to this panel box are the storage batteries with charging board used in electric checks. On the south side of the room, where the door is situated, enough space has been left to wheel a stretcher with a patient to the front of the calorimeter. By making careful use of every inch a great deal of apparatus has been placed in a small room without crowding those who work there.

### THE FRAME

As the photographs show, the calorimeter was made high enough at the head to allow the subject to sit upright. This increases the

5. Langworthy and Milner: Year Book U. S. Dept. Agriculture, 1910, p. 307; ibid., 1911, p. 491.

6. Benedict, F. G.: Ein Universalrespirationsapparat, Deutsch. Arch. f. klin. Med., 1912, cvii, 156.

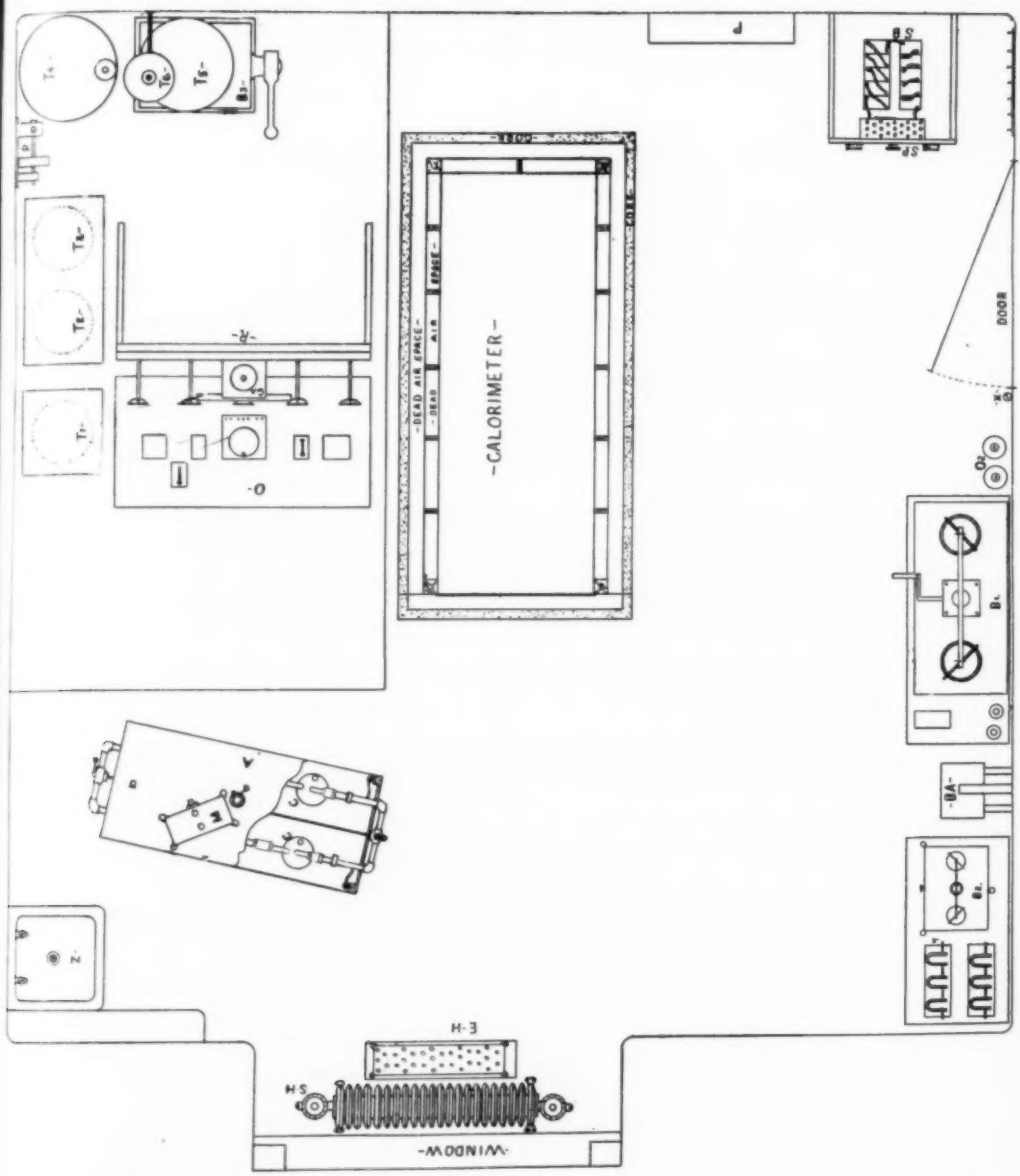


Fig. 3.—The calorimeter room. A, Absorber table. M. Bohr meter. b, Drying tower for air sample drawn through meter. CC, Williams bottles containing sulphuric acid. SH, Steam heater. EH, Electric heater. Z, Sink. O, Observer's table. Ga, Galvanometer. R, Rheostat board. $T_1$, Gouy regulator tank. $T_2$, Ice tank for cooling water running through absorber in calorimeter. $T_3$, Ice tank for water to cool outer copper wall. $T_4$, Large supply tank. $T_5$, Tank on platform balance ($B_2$) for weighing water. $T_6$, Small tank to hold water from absorber while $T_5$ is being weighed. p, Pump to lift water from $T_4$ to constant-level tank near the ceiling. P, Panel box. S B, Edison storage batteries. SP, Charging panel. x, Pyrene fire extinguisher. $O_2$, Oxygen tanks. $B_1$, Balance for sulphuric bottles, etc. Ba, Barometer. $B_2$, Balance for U-tubes.

volume of contained air and magnifies certain errors, but makes the box much more comfortable and apparently gives better results than if the quarters were cramped. The frame (Fig. 4) was made of wood, as previous experience with the small calorimeter in Cornell had shown that the mass of angle iron between the metal walls made the box very sluggish in responding to temperature changes. To prevent warping, which would be disastrous, the best quality white pattern pine was used and the frame allowed to stand for several months before it was shellacked. The outside timbers were 6.35 by 6.35 cm. square and the braces 6.35 by 1.9 cm. All joints were glued and dowelled. The braces were spaced 30.48 cm. apart to give rigidity to the copper walls which are attached to the wood in many places.

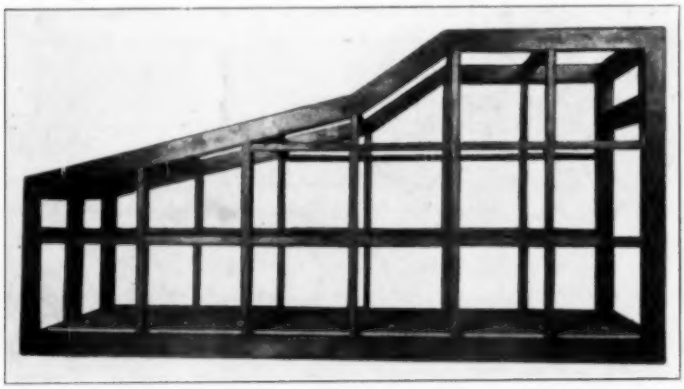

Fig. 4.—Wooden frame of calorimeter with asbestos board as floor.

### COPPER WALLS

The inner copper wall (Fig. 5) forms an air-tight box 198.18 cm. long, 76.2 cm. wide, 91.4 cm. high at one end and 45.7 cm. at the other, with a capacity of 1,123 liters. At the head is an opening to serve as a door and on one side an opening for a window.

The wall is made of "16-ounce" sheet copper, tinned on the inside. It is fastened to the inner side of the wooden frame by means of brass angles soldered to the copper and screwed to the wood. The bottom rests on a long slab of asbetos board 9.5 mm. thick.

The outer copper wall (Fig. 6) which is screwed directly on the outer side of the wooden frame, does not come in metallic contact with the inner wall at any place except the rim around the large opening at the head of the box. This outer wall is made of "14-ounce" copper tinned on the outside, and while the joints are soldered they are not necessarily air-tight.

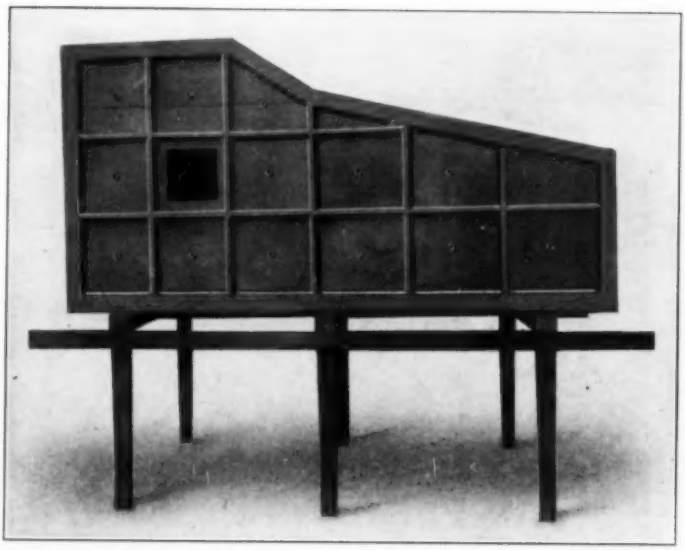

Fig. 5.—Inner copper box with brass thimbles for thermopiles.

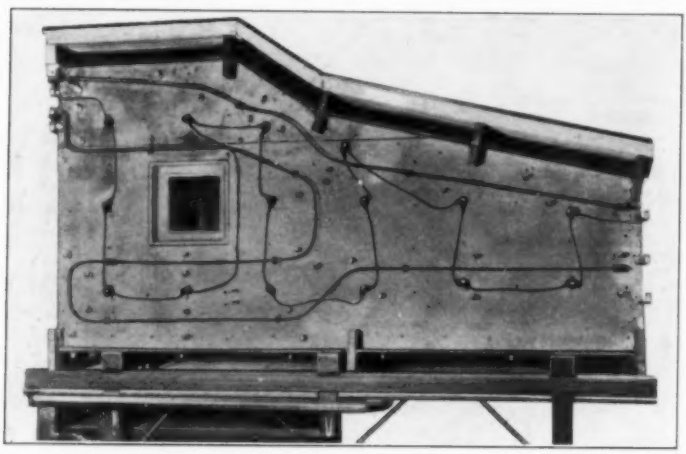

Fig. 6.—Outer copper box with leads connecting thermopiles, pipes for cold water and porcelain insulators for resistance wires. The wires themselves are not shown in the photograph. The top and bottom of the wooden box are in position.

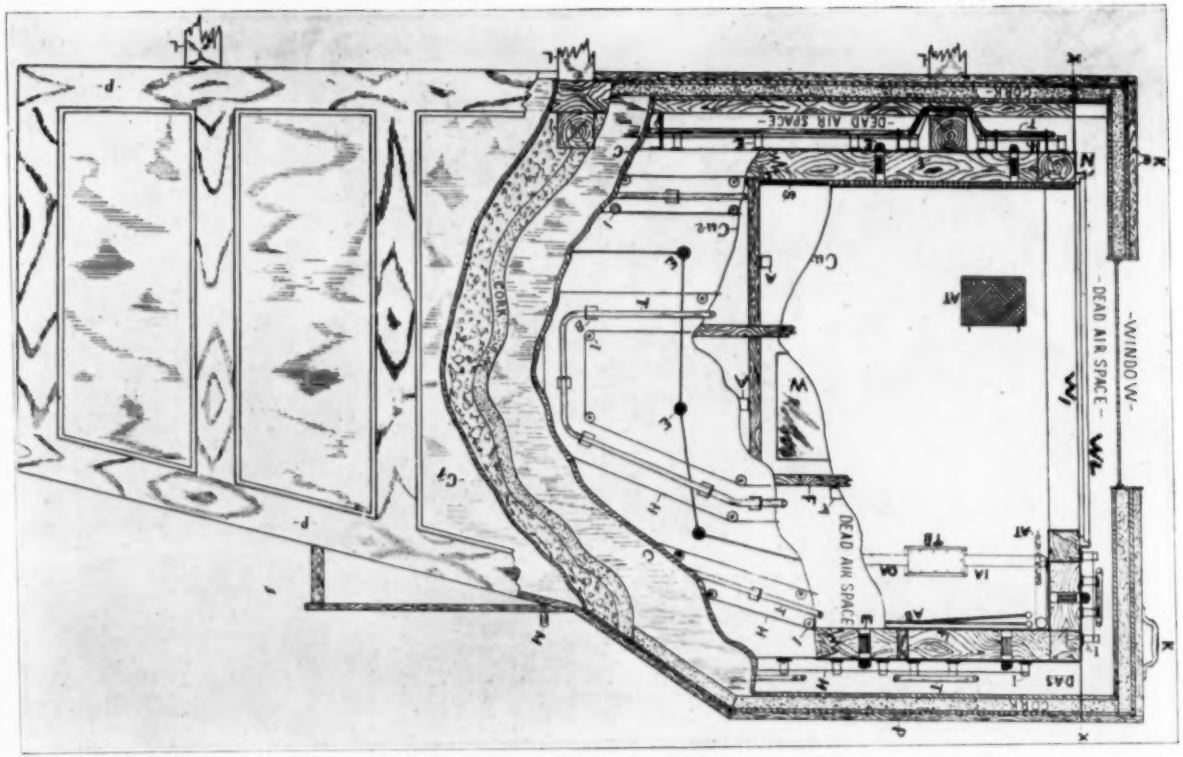


Fig. 7.—Sectional view of the calorimeter. AA, Brass angles fastening inner copper wall to wooden frame. AT, Air thermometer. AB, Heat absorber pipes. BB, Brass angles supporting cold water pipes on the outer copper wall. C, Inner layer of "Compo Board." $C_1$ Outer layer "Compo Board." Cu, Inner copper wall. Cu2, Outer copper wall. DAS, Dead air space. EE, Thermopiles. F, Wooden frame. H, Resistance wire. I, Porcelain insulators. IA, Ingoing air pipe. K, Handles of wooden panel at head of box removed at line X - X. L, Wooden legs of calorimeter. M, Pipe leading from interior of box to spirometer. N, Copper frame in which are placed glass plates $W_1$ and $W_2$. OA, Outgoing air pipe. P, Wooden supports for "Compo Board." S, Asbestos board under floor of calorimeter. TT, Cold water pipe. W, small window.

The braces of the wooden frame divide the dead air space between the walls into compartments about 30.48 cm. square and 6.35 cm. thick. In the center of each compartment is placed a thermopile with four thermocouples in thermal but not in electrical contact with each copper wall. The inner end of this thermopile fits in a brass thimble 25.4 mm. deep soldered to the outer side of the inner wall. The outer end (with its four thermocouples) fits in a brass tube which passes through the outer wall and is closed off from the outside air by P. B. Compound and electric tape.

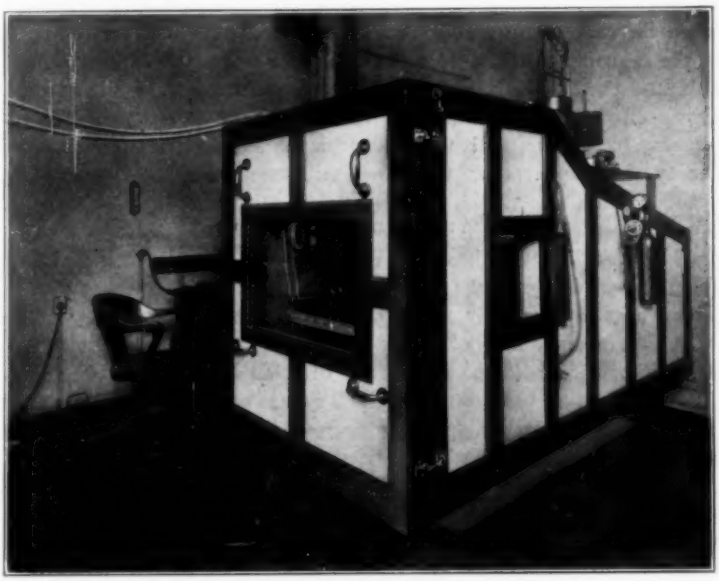

Fig. 8.—Calorimeter with front closed.

In Figure 13 the large opening at the head of the box, measuring 76 by 70 cm., is closed by two glass plates 7.5 mm. thick, each sealed after the subject has entered the calorimeter by means of a mixture of 5 parts bees-wax and 1½ parts Venice turpentine. The small window in Figure 6 is permanently closed by glass plates fastened to the copper walls. There are numerous pipes and electric cables entering the box as will be described later.

On the surface of the outer copper wall are attached the wires connecting the thermopiles. The pipes for cold water are swung on brass angles attached to this surface and the enameled "Therlo" resistance wire is bound on insulators to the same surface, very much as described by Benedict and Carpenter.

### INSULATING WALL

Completely surrounding the outer copper wall and separated from it by a space of 7 cm. is the thick wall intended to protect the calorimeter from fluctuations in the room temperature. This is constructed of a layer of pressed cork 2.54 cm. thick, between two layers of "Compo Board," a patented building material made of strips of wood glued between layers of stout paper. This is supported by a framework of white-wood, making panels which are light, yet very effective as heat insulators. The head of the wooden box is provided with a glass window and furnished with handles so that it can be easily removed when the experiment is over and placed on a small shelf on the right of the calorimeter. The frame of this outer box is stained to resemble oak, and the "Compo Board" panels are painted with white enamel. Every effort has been made to make the room and the calorimeter pleasing to the eye, with the result that patients are attracted by the beauty of the apparatus rather than by its resemblance to a coffin.

### THE ABSORBER TABLE

The absorber table is so arranged that the air current is switched from one set of absorbers to the other by means of a three-way valve. This works satisfactorily and is much quicker than the old style seat-valves. The sulphuric bottles are larger models of the form described by Williams and hold about 1¼ liters of acid, which will remove every trace of moisture until more than 100 grams has been absorbed. The soda-lime bottles resemble those devised by Benedict,[6] except for a modification of the tube which carries the entering air. This is divided in such a manner that the soda-lime can be packed about a brass pipe, the lower end of which is perforated and the upper end of which reaches almost to the top of the bottle, where it fits snugly in an elbow attached to the stopper. The Crowell blower is the same as the ones used by Williams and Benedict, but a safety device has been attached to prevent accidental reversal of the blower which would have disastrous effects. The two small bicarbonate cans next to the last sulphuric bottle did not remove entirely the acid vapors and it was necessary to place a long cylinder in the vertical pipe which carries the air from the absorber table. This contains about 340 grams of bicarbonate of soda packed between layers of cotton and catches all traces of acid fumes.

The air enters the box in a pipe which ends in a single opening directed just above the subject's head and leaves through a number of small openings in a pipe which runs across the foot of the box. A small electric fan at the lower end of the calorimeter keeps the air well stirred.

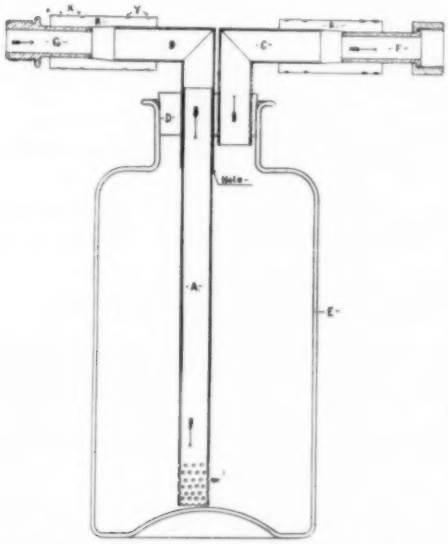


Fig. 9.—Modified soda-lime bottle. A, Brass tube with perforated bottom and top which fits in brass elbow, B. The bottle is filled with A in position and the rubber stopper D with elbows B and C is then forced into neck of bottle. G and F, Brass couplings. R and $R_1$, heavy rubber tubing. X and Y, Binding wires.

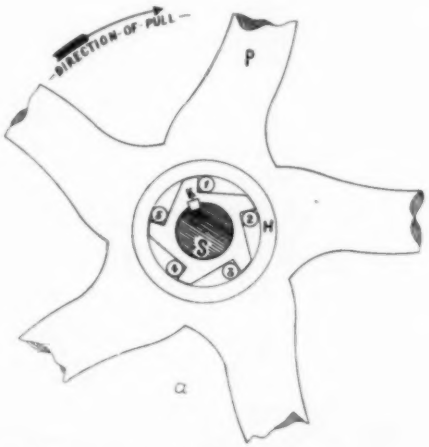


Fig. 10.—Safety device to prevent blower from being reversed. P, Pulley for belt to motor. S, Shaft of blower. H, Hub of wheel. K, Key 1, 2, 3, 4, 5, hardened steel rollers which engage when pulley is running in right direction, but disengage when pulley starts in opposite direction.

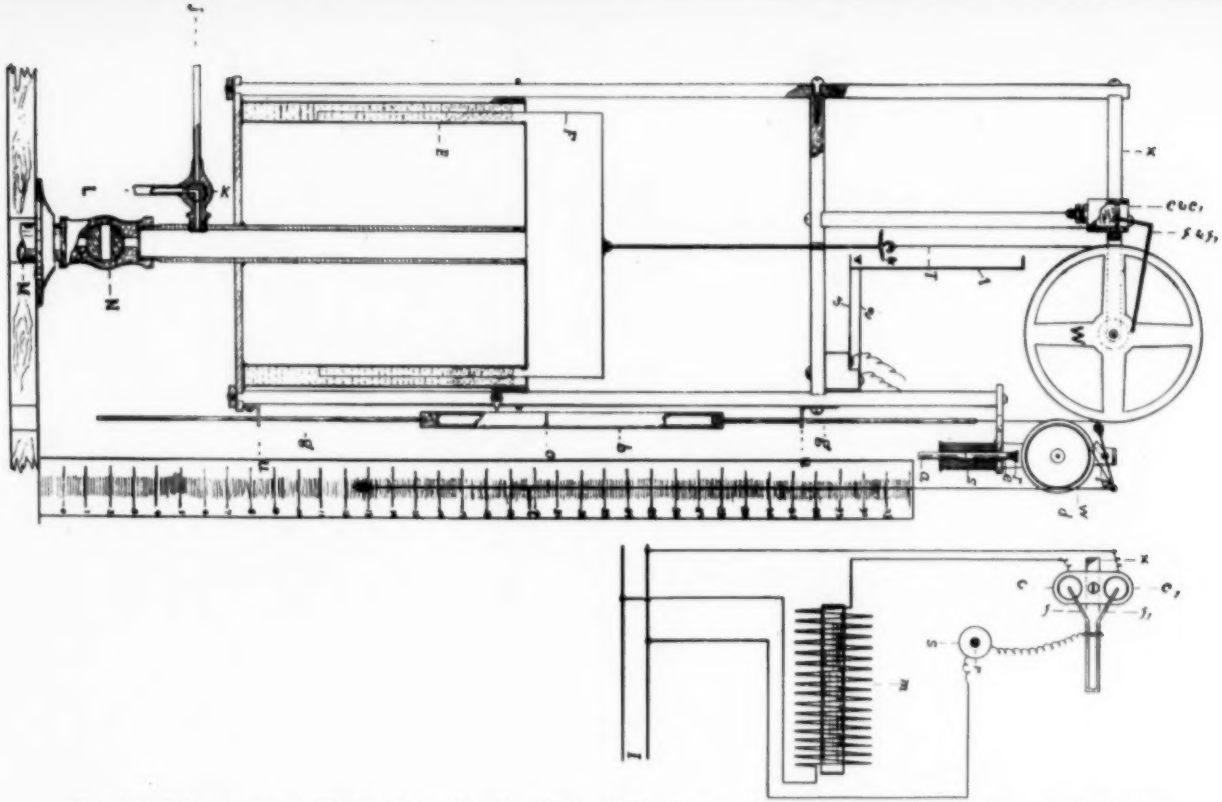

Fig. 11.—Spirometer and Work-Adder. M, Pipe from calorimeter to spirometer. N, two-way valve. J, Small pipe to ingoing air pipe. L, Oxygen inlet. K, Three-way valve arranged to admit oxygen into ingoing air pipe or into spirometer. E, Spirometer tank filled with water. F, Spirometer bell of light copper. T, String supporting bell. W, Wheel supporting bell. b, Counterpoise filled with mercury. gg, Guiding rod fitting loosely in uu. o, Mark on counterpoise. The spirometer is filled at the end of each period until this mark is opposite the pointer. w, Work-adder with toothed edge and cam. d, Drum on which is wound the thread t. P, Small lever with eye through which thread passes. When the thread is pulled downward the cam is lifted. s, Solenoid. r, e, a, Plunger which is raised by solenoid, pressing against edge of work-adder while the spirometer bell is being raised by the admission of oxygen. r, Soft rubber; e, hard rubber; a, iron. x, brass support. c and $c_1$, mercury cups into which dip f and $f_1$ when the spirometer bell sinks, making contacts which raise plunger and energize magnet m, thus admitting oxygen. I, Low voltage current corresponding to I, of Fig. 15. 1, 2, 3, 4, Automatic alarm which rings a bell whenever spirometer rises dangerously high or sinks too low. 4, A button on the rod supporting spirometer bell makes contact between 2 and 3 either by raising hook 1, connected with 3, or by depressing the small triangular knob connected with 2.

The spirometer on the top of the calorimeter resembles Benedict's[6] except that it is provided with a work-adder to record movement of the patient and not the total ventilation of the lungs. The bell is made of very light copper, is suspended in water and is carefully counterpoised. The counterpoise is provided with a writing point which records on a smoked paper the movements of the drum. To the wheel at the top is attached a brass arm with two points which dip into mercury cups set at slightly different levels whenever the spirometer bell

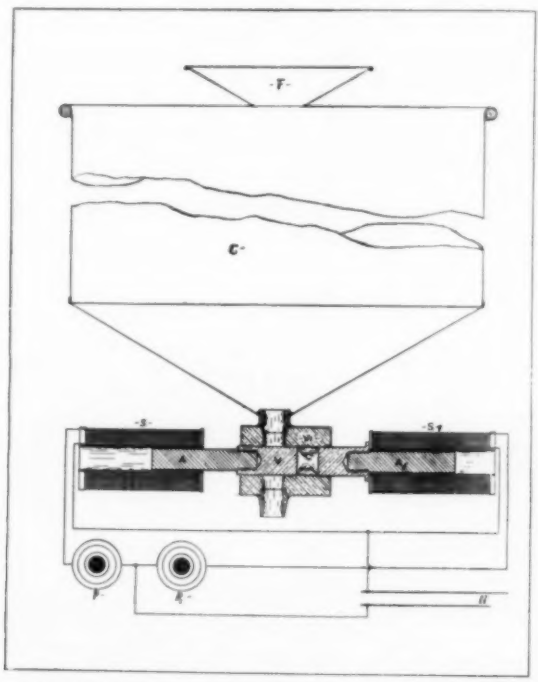


Fig. 12.—Electrical device for shutting and opening valve P. $P_1$. Push buttons controlling solenoids S and $S_1$. A and $A_1$ iron cores attached to brass rod V. Valve is shown closed. When current is passed through S the Rod V will be drawn to the left and the narrow portion seen just under $V_1$ will come opposite the pipe leading from receiving can G.

sinks below a certain mark. One of these cups operates a magnet which opens the attachment that automatically admits the oxygen. This keeps the spirometer within about one centimeter of the same level unless the subject moves and suddenly heats the air locally. It is remarkable how promptly the spirometer rises when the person within the box makes even a slight movement of a hand or leg. In fact, it makes so delicate a

movement recorder that a Porter work-adder has been attached in such a manner that the downward movement of the counterpoise winds up a thread and the total amount of thread so wound represents the total work done by the patient during that particular period. By standardizing various movements of the body such as turning over or lifting the arm it is possible to gain a fairly accurate idea of the amount of mus-

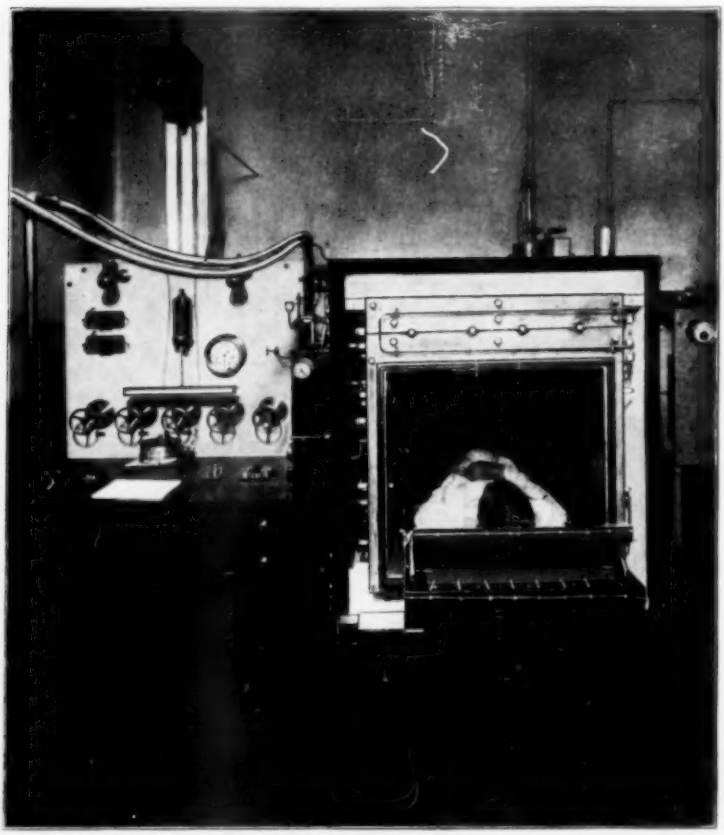

Fig. 13.—View of open calorimeter. Patient on canvas bed partly in the chamber. On the left can be seen the observer's table and the rheostat board with the galvanometer. The rubber pipes for outgoing and ingoing air lead to the absorber table, a corner of which can be seen on the extreme left. In the background on the right are the storage batteries and charging panel.

cular movement and express it in centimeters of thread, thus obviating the necessity of printing long graphic records. In order to prevent the work-adder from winding up thread while the oxygen is being admitted,

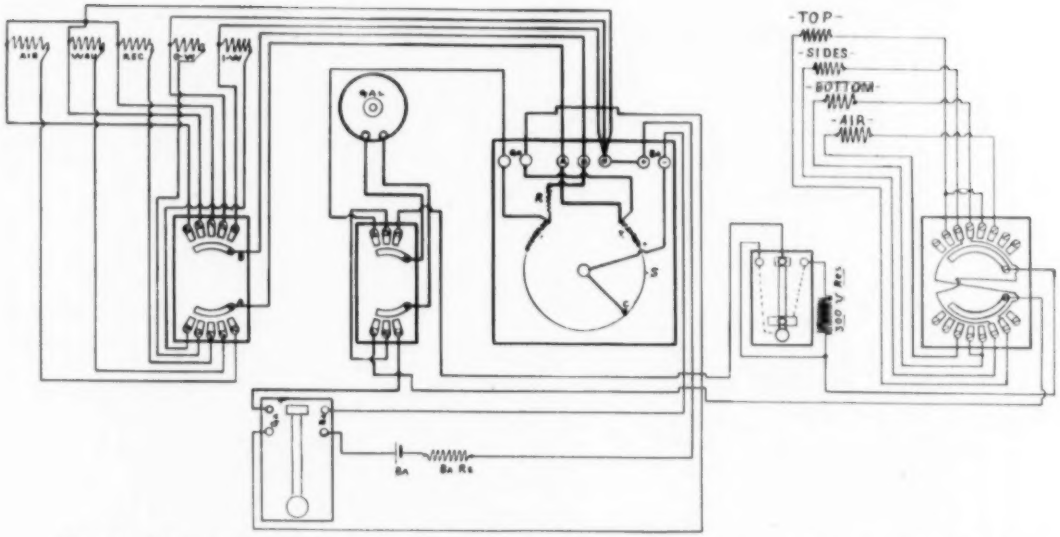


Fig. 14.—Wiring diagram of observer's table. In the center is the Kohlrausch bridge, to the right a tapping key with an arrangement for throwing in 300 ohms resistance when needed. This key is used in reading the thermopiles connected with the switch on the right. To the left of the bridge is a switch for connecting either thermopiles or resistance thermometers with the galvanometer. On the extreme left is the switch for the air, wall, rectal, ingoing and outgoing water thermometers, each of which contains 100 ohms. Since this diagram was made two additional thermometers for surface temperature have been added. In the front of the table is a tapping key.

a solenoid is connected with the second mercury cup into which the brass arm on the wheel dips. This solenoid operates a small plunger which holds the work-adder while the magnet opens the oxygen valve and also maintains its hold for the instant after the oxygen has been shut off, since the spirometer rises somewhat slowly after the admission of oxygen. This solenoid lag, which corresponds to the spirometer lag, is secured by having the second mercury cup filled slightly more than the cup which controls the oxygen magnet.

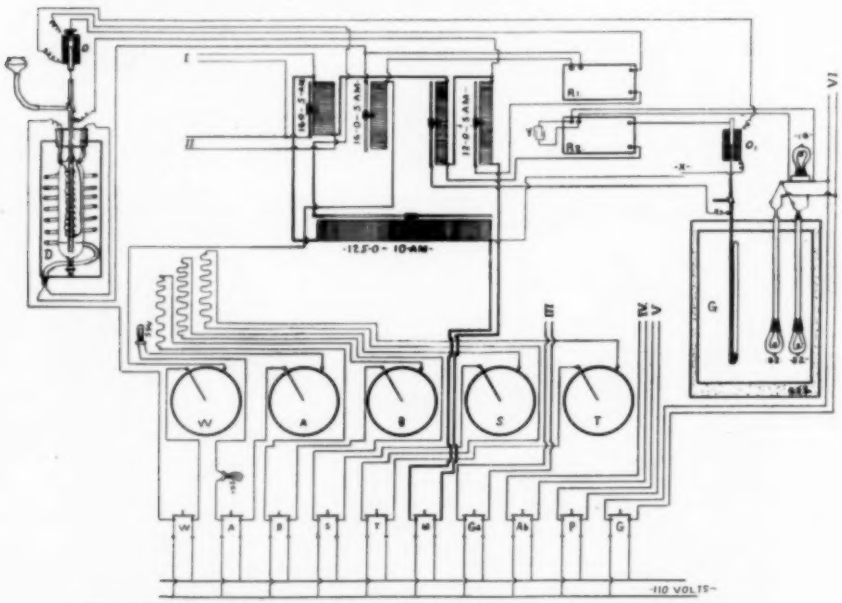


Fig. 15.—Wiring diagram of rheostat board. W, Switch and rheostat to control temperature of ingoing water in water heating resistance, D. A, Ingoing air. B, Bottom of calorimeter. S, Sides. T, Top. Ga, Galvanometer lamp. Ab, Motor on absorber table. P, Motor for pump. G, Lamps in Gouy regulator. M, Miscellaneous parts connected with tube rheostats. O, $O_1$, Solenoid agitators lifting and dropping platinum contacts with mercury in Gouy and current regulator as the contact is made and broken mechanically at x. $R_1$, Relay for current regulator. $R_2$, Relay to control heating of lamps in Gouy.

The heat-absorbing system is the same as that described by Williams, the Gouy regulator and Williams' water heating resistance and current regulator giving very satisfactory results. The water coil suspended from the roof of the calorimeter has, however, been wound with brass "jack chain" to increase its absorbing surface. From this coil the water runs to the weighing tank on the platform of a "silk scale"

which is sensitive within 10 grams. The flow of water was formerly cut off by hand at the end of each period, but this is now done by a pair of solenoids controlled by the operator at the observer's table, thus reducing the staff by one man. The stream of water runs constantly through a can which has the capacity of 10 liters, and is provided at its lowest point with a valve that is opened and shut by the pair of solenoids above mentioned. At the end of a period the valve is shut and the water collects in the can while the tank is being weighed. After the weighing is finished the valve is opened and the water runs once more into the tank.

### RHEOSTAT BOARD AND OBSERVER'S TABLE

The marble rheostat board and the observer's table resemble closely those described by Williams. This rheostat board, the panel box, charging panel for the storage batteries, conduits, wires, etc., were installed by the Electric Construction Supply Company after specifications kindly drawn up for us by the Department of Water Supply, Gas and Electricity of New York City. Directly above the rheostat board is mounted a galvanometer of the d'Arsonval type, provided with prisms so that the ascending ray of light from the lamp below is reflected from the mirror of the galvanometer downward to a scale just above the table. (Siemans and Halske.) This vertical mounting with scale that can be read by daylight saves a great deal of room. The galvanometer is braced securely and does not vibrate. To protect it from the dust it is covered with a thin copper hood. The resistance of the moving system is 45 ohms and there is a ballast resistance of 200 ohms in series, which, however, is not used.

Most of the precision switches used were furnished by Siemans and Halske, Catalogue Number 17327. One of similar design was made in our own shop. A new device which has given great satisfaction has been introduced into the switch connecting thermopiles with galvanometer. At the start of the experiment, or at any other time when the temperature differences between outer and inner walls are large, a resistance of 300 ohms is kept in series. As soon as the calorimeter is in balance a button on the switch is turned and the resistance short-circuited, making the adiabatic control extremely delicate. The Kohlrausch bridge provided by the Leeds and Northrup Company of Philadelphia is similar to the one described by Williams. The 60-step rheostat for controlling the temperature of the ingoing water and the four 45-step rheostats controlling that of the ingoing air, bottom, sides and top of the outer copper wall, were made by the Simplex Heater Company of Cambridge, Mass. They are mounted on the back of the board with their handles projecting through the board to the observer's

table. Just above them on the back of the marble slab are the five tube rheostats (Siemans and Halske) used to cut down the current to various small pieces of apparatus. On the front of the board are the two relays, one for the Williams water heating resistance and current regulator and the other for the Gouy regulator.

The thermopiles between outer and inner copper walls are arranged in three groups, thirty-two on the top, thirty on the sides and twelve on the bottom, the area covered by each group being warmed by a strand of enamelled "Therlo Wire," No. 24 B & S gauge, whose temperature is controlled by one of the step rheostats.

One thermopile is arranged with one end in the outgoing air current and the other in the ingoing air. The temperature of the latter is adjusted to that of the former by means of a step rheostat and two 55 volt lamps. A similar rheostat controls the temperature of the ingoing water by means of the water heating resistance.

### THERMOMETERS

All thermometers contain 100 ohms resistance in nickel or platinum wire and are made on the three-lead system, being read on the same galvanometer used for the thermopiles. The water thermometers made by Leeds and Northrup are similar to those constructed by them for the automatic calorimeter of the Department of Agriculture. They are described in the Leeds and Northrup catalogue (Bulletin 811) and also by Dickinson and Mueller[7] of the United States Bureau of Standards. In our hands they have been most satisfactory, since they are more accurate, easier to calibrate, and easier to read than mercurials. The Leeds and Northrup air thermometer, similar to that used by Williams, is in eight divisions scattered over the inside of the box so as to give the average temperature of the air. They are connected in series by copper wire covered with rubber and a casing of lead, a combination made especially for us which has given good service. The wall thermometer consisting of eight divisions in series was made in this laboratory. Each division was made of No. 38 double silk covered nickel wire wound around a strip of mica and held 2 or 3 mm. from the inside of the inner copper wall. Over this was soldered a shallow copper box so that the resistance wire would lie in a small air space completely surrounded by metal at the temperature of the wall.

The rectal thermometer is of a new design made to respond more rapidly to changes in the temperature than the old type in which the resistance wire was surrounded by a jacket of dead air. The nickel wire with its double silk covering is wound on a small piece of ivory

7. Dickinson and Mueller: New Calorimetric Resistance Thermometers, Bull. Bureau Standards, 1913, ix, 483.

and dipped in a round ended silver tube filled with molten Wood's fusible alloy at a temperature of 96 C. This is solidified by dipping in water, thus forming direct metallic contact between the outside of the silver tube and the insulated wire. The leads from the thermometer are enclosed in a soft rubber tube. The surface thermometers are made of flat circular buttons of ivory 25 mm. in diameter and 5 mm. thick. One side of the button is hollowed out to a depth of 3 mm., the edges being filleted. On the bottom of this depression is wound concentrically the resistance wire. On this is poured the molten Wood's metal until it is flush with the original level of the ivory. Two of these units are used in series in each of the two surface thermometers. They are strapped to the skin with adhesive plaster and covered with a pad of cotton wool about 20 cm. in diameter and 4 cm. thick, this also being held in place with adhesive plaster.

The air thermometers were calibrated by the makers and the wall thermometers made to contain exactly the same resistance. Since they are used only to denote relative changes in temperature, a more exact calibration is not necessary. The rectal, surface and water thermometers are standardized several times a year by means of very accurate mercurials, certified by the Physikalische Technische Reichsanstalt. When calibrating them one notices that the electric thermometers all respond to temperature changes much more quickly than the mercurials.

The flexible rubber covered leads from the surface and rectal thermometers and the lead covered wires from the wall and air thermometers are carried to a ten-wire cable which perforates the calorimeter walls and is distributed on a hard rubber plate attached to the calorimeter and thence carried to the switches on the observer's table. The high tension currents from the calorimeter pass to a small hard rubber plate inside the box, thence in a separate strand cable to a slate board outside the calorimeter, and thence to the rheostat board. This cable carries leads for the telephone, electric fan and for the resistance coil used in electric checks.

### ACCESSORY APPARATUS

The telephone, which has been made as light as possible, is seldom used, since the muscular work involved in telephoning is enough to affect seriously the results in rest experiments. The small electric fan placed in a corner at the foot of the calorimeter stirs the air thoroughly and allows one to get a good sample by drawing off ten liters through the large Bohr meter attached to the outgoing air pipe. The fan is run by the Edison storage batteries, giving off approximately 4.5 calories an hour, the exact amount being determined once an hour by a voltmeter and ammeter.

On the right side of the subject is a small glass shelf for the weighed urine bottles which, after each voiding, are placed on a spring balance that can be read through the window. Two small brass tubes are led through the wall of the calorimeter just below the small window. One acts as an emergency vent to prevent a positive or negative pressure at the beginning or end of an experiment when the ventilation is stopped. To the other is attached the Bowles stethoscope, which is strapped over the apex of the heart so that an observer outside can count the pulse at frequent intervals.

The inside of the calorimeter is formed by the polished tinned copper, the roof being almost hidden by the longitudinal absorber pipes wound with brass "jack chain." The calorimeter is wide enough for a man to turn comfortably from side to side, high enough at the foot to allow him to cross his legs and high enough at the head to allow him to sit upright.

### THE BED

The bed in its present form is the result of much experimentation. The frame is made of varnished oak raised at the head so that the top is 12.7 cm. from the floor of the calorimeter while it is raised only 8.2 cm. at the foot. This allows for the sag of the waterproof canvas laced in the frame and keeps the subject 2 to 3 cm. from the copper floor. At the head is a back-rest with a piece of water-proof canvas, which is usually supplemented by a soft pillow. The bed is mounted on a pair of skids so that it can be pushed from the stretcher into the box. The canvas has proved to be much more comfortable than the springs and blankets formerly employed and has the advantage of absorbing very little water vapor. The varnished wood absorbs some water, the necessary clothing of the patient a great deal more, while the polished walls absorb only a minimum.

### ELECTRIC AND ALCOHOL CONTROL EXPERIMENTS

The calorimeter has been tested repeatedly by dissipating known amounts of heat in resistance coils and by burning known amounts of alcohol. The apparatus and procedure used correspond almost exactly with those described by Williams and are similar to those previously used by Atwater and Benedict and by Benedict, Riche and Emmes.[8] In calculating the latent heat of the evaporation of water we have adopted the figures of Smith[9] and have given the latent heat the value of 0.584 large calories per gram of water evaporated at 23 C., the usual experimental temperature.

8. Benedict, Riche and Emmes: Control Tests of a Respiration Calorimeter, Am. Jour. Physiol., 1910, xxvi, 1.
9. Smith, A. W.: Heat of Evaporation of Water, Physical Review, 1907, xxv, 145.

TABLE I.—Alcohol Chicks.*

| Date and Per Cent. Alcohol by Weight | Hour | Heat | | | | Oxygen | | | Carbon Dioxid | | | Water | | | R. Q. Theory, 0.667 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Alcohol Burned, Gm. | Theory, Cal. | Found, Cal. | Error, Per Cent. | Theory, Gm. | Found, Gm. | Error, Per Cent. | Theory, Gm. | Found, Gm. | Error, Per Cent. | Theory, Gm. | Found, Gm. | Error, Per Cent. | |
| 3/8/13 92.28 | 1 | 10.14 | 66.25 | 64.52 | −2.6 | 19.53 | 19.11 | −2.2 | 17.99 | 17.81 | −0.5 | 11.76 | 12.92 | +9.8 | 0.662 |
| | 2 | 10.08 | 65.86 | 65.86 | ±0.0 | 19.41 | 18.08 | −6.9 | 17.79 | 18.18 | +2.3 | 11.69 | 11.82 | +1.1 | 0.715 |
| | 3 | 9.85 | 64.62 | 64.29 | −0.0 | 19.05 | 19.17 | +0.6 | 17.46 | 17.44 | −0.1 | 11.47 | 11.56 | +0.8 | 0.662 |
| | 4 | 9.43 | 61.61 | 60.49 | −1.8 | 18.16 | 17.99 | −0.8 | 16.65 | 16.48 | −1.0 | 10.94 | 11.10 | +1.4 | 0.666 |
| Average | .. | ..... | 64.52 | 63.79 | −1.1 | 19.04 | 18.59 | −2.4 | 17.45 | 17.48 | +0.2 | 11.47 | 11.85 | +3.4 | 0.676 |
| 4/30/13 91.60 | 1 | 8.42 | 54.60 | 56.06 | +2.7 | 16.09 | 16.61 | +3.2 | 14.75 | 14.73 | −0.1 | 9.75 | 10.29 | +5.5 | 0.644 |
| | 2 | 8.19 | 53.04 | 52.59 | −0.8 | 15.65 | 15.43 | −1.4 | 14.35 | 14.30 | −0.4 | 9.48 | 10.01 | +5.6 | 0.674 |
| | 3 | 8.14 | 52.79 | 51.86 | −1.7 | 15.56 | 15.39 | −1.1 | 14.26 | 14.37 | +0.8 | 9.42 | 9.94 | +5.5 | 0.680 |
| | 4 | 8.04 | 52.14 | 51.37 | −1.6 | 15.37 | 15.23 | −0.9 | 14.08 | 13.82 | −1.8 | 9.31 | 9.55 | +2.5 | 0.660 |
| Average | .. | ..... | 53.14 | 52.97 | −0.3 | 15.67 | 15.67 | ±0.0 | 14.36 | 14.31 | −0.4 | 9.49 | 9.95 | +4.8 | 0.665 |
| 10/14/13 90.96 | 1 | 12.24 | 78.83 | 76.50 | −3.0 | 23.22 | 23.20 | −0.1 | 21.29 | 21.34 | +0.2 | 14.15 | 14.73 | +4.1 | 0.669 |
| | 2 | 12.36 | 79.60 | 80.48 | +1.1 | 23.45 | 24.82 | +5.8 | 21.50 | 21.98 | +2.3 | 14.29 | 14.83 | +3.7 | 0.644 |
| | 3 | 11.86 | 76.37 | 73.78 | −3.3 | 22.50 | 20.55 | −8.6 | 20.63 | 19.98 | −3.0 | 13.71 | 13.53 | −1.4 | 0.707 |
| Average | .. | ..... | 78.27 | 76.92 | −1.7 | 23.06 | 22.86 | −0.8 | 21.14 | 21.10 | −0.2 | 14.05 | 14.36 | +2.2 | 0.673 |
| 2/2/14 91.18 | 1 | 9.22 | 59.52 | 59.82 | +0.5 | 17.54 | 17.62 | +0.5 | 16.07 | 15.65 | −2.7 | 10.43 | 10.85 | +4.0 | 0.646 |
| | 2 | 9.29 | 59.97 | 61.29 | +2.2 | 17.67 | 16.78 | −5.0 | 16.20 | 15.75 | −2.8 | 10.51 | 10.71 | +1.9 | 0.682 |
| | 3 | 8.59 | 55.45 | 56.23 | +1.5 | 16.34 | 15.98 | −2.2 | 14.98 | 15.07 | +0.6 | 9.72 | 10.30 | +6.0 | 0.686 |
| | 4 | 9.70 | 62.62 | 64.05 | +2.3 | 18.45 | 18.24 | −1.2 | 16.91 | 16.82 | −0.5 | 10.97 | 11.32 | +3.2 | 0.671 |
| Average | .. | ..... | 59.39 | 60.35 | +1.6 | 17.50 | 17.16 | −1.9 | 16.04 | 15.82 | −1.3 | 10.41 | 10.80 | +3.8 | 0.671 |
| 3/19/14 91.18 | 1 | 10.41 | 67.20 | 67.34 | +0.2 | 19.80 | 19.41 | −2.0 | 18.15 | 18.23 | +0.4 | 11.77 | 12.02 | +2.0 | 0.683 |
| | 2 | 11.02 | 71.14 | 69.43 | −2.4 | 20.96 | 19.33 | −7.7 | 19.21 | 18.14 | −5.6 | 12.46 | 12.13 | −2.6 | 0.683 |
| | 3 | 10.89 | 70.30 | 70.36 | +0.1 | 20.71 | 19.53 | −5.7 | 18.99 | 18.61 | −2.0 | 12.32 | 12.62 | +2.5 | 0.693 |
| | 4 | 10.04 | 64.81 | 66.29 | +2.3 | 19.10 | 20.13 | +5.4 | 17.50 | 17.75 | +1.4 | 11.36 | 11.95 | +5.2 | 0.641 |
| Average | .. | ..... | 68.36 | 68.36 | ±0.0 | 20.14 | 19.60 | −2.6 | 18.46 | 18.18 | −1.5 | 11.98 | 12.18 | +1.7 | 0.675 |
| Total.... | .. | ..... | 1216.72 | 1212.61 | −0.33 | 358.56 | 325.60 | −1.69 | 328.67 | 326.45 | −0.68 | 215.52 | 222.18 | +3.09 | Av. 0.672 |

* All periods one hour long.

It has seemed advisable to publish all the electric and alcohol checks made with the calorimeter. In publishing control tests the results are much more striking if one selects only the best and leaves out those in which the agreement is not close. This method expresses only the minimum error while the things we really need to know are the average, maximum and total errors. The total error shows the accuracy of the method, the maximum error may occur in the course of any experiment, while the average error is with us always. The minimum error

TABLE 2.—ELECTRIC CHECKS

| Date | Length of Period, Min. | Calories, Theory | Calories, Found | Per Cent. Error | Date | Length of Period, Min. | Calories, Theory | Calories, Found | Per Cent. Error |
|---|---|---|---|---|---|---|---|---|---|
| 3/4/13 | 60 | 72.25 | 73.19 | +1.3 | 11/28/13 | 60 | 78.22 | 77.15 | −1.4 |
| | 60 | 72.25 | 72.19 | +0.0 | | 60 | 78.22 | 77.62 | −0.8 |
| Average | .. | 72.25 | 72.69 | +0.6 | | 60 | 78.22 | 78.67 | +0.6 |
| 4/5/13 | 60 | 80.78 | 77.26 | −4.4 | Average | .. | 78.22 | 77.81 | −0.5 |
| | 60 | 80.78 | 79.81 | −1.8 | 1/26/14 | 60 | 76.92 | 75.86 | −1.4 |
| Average | .. | 80.78 | 78.29 | −3.1 | | 60 | 76.92 | 77.41 | +0.6 |
| 10/13/13 | 30 | 41.74 | 42.15 | +1.0 | | 60 | 76.92 | 77.88 | +1.3 |
| | 30 | 41.74 | 41.56 | −0.4 | | 60 | 76.92 | 77.24 | +0.4 |
| | 30 | 41.74 | 41.25 | −1.2 | Average | .. | 76.92 | 77.10 | +0.2 |
| | 30 | 41.74 | 41.10 | −1.5 | | | | | |
| | 30 | 41.74 | 41.35 | −0.8 | 5/11/14 | 60A | 78.71 | 80.03 | * |
| Average | .. | 41.74 | 41.49 | −0.6 | | 60B | 78.22 | 75.18 | .... |
| 10/22/13 | 60 | 83.98 | 83.98 | ±0.0 | | 30C | 39.07 | 41.35 | .... |
| | 60 | 83.98 | 83.83 | −0.2 | Total.... | 150 | 196.00 | 196.56 | +0.3 |
| | 60 | 83.98 | 84.02 | +0.0 | | | | | |
| | 60 | 83.98 | 83.84 | −0.2 | Total of all checks | .. | 1589.02 | 1583.42 | −3.5 |
| Average | .. | 83.98 | 83.92 | −0.1 | | | | | |

* A, B, C. Temperature changes of wall of calorimeter: A, +0.06 C.; B, −0.73 C.; C, −0.05 C. Test to verify hydrothermal equivalent.

is a joy to behold, but it does not occur with the regularity inferred by the prominence it is usually given. If, for instance, we should publish only the electric check of October 22 with an hourly error of 0.2 per cent., and the alcohol check of April 30, in which the total errors in the measurement of heat, oxygen and carbon dioxid are all less than ½ of 1 per cent., we should give a false impression of accuracy. This test shows that the calorimeter is capable of measuring heat, oxygen and carbon dioxid with a maximum error of 1.8 per cent. in three consecutive hours. Even better results could be obtained if greater care were taken to secure an even combustion of alcohol. On the other

hand, the errors which can occur in hourly periods and in whole experiments are shown in Table 3. The average error has been obtained by multiplying each per cent. of error by the number of times it occurs and dividing the total by the number of periods. In the whole series of experiments of three or four hours' duration the average error for heat is 0.9 per cent., for oxygen 1.6 per cent. and for carbon dioxid 0.6 per cent., while for the individual hours the error is 1.2 per cent., 3.2 per cent. and 1.6 per cent., respectively. The total error in all the

TABLE 3.—SUMMARY OF ERRORS IN ELECTRIC AND ALCOHOL CHECKS

| Per Cent. Error | Average of Whole Experiment | | | | Individual Hours | | | |
|---|---|---|---|---|---|---|---|---|
| | Cal. | $O_2$ | $CO_2$ | $H_2O$ | Cal. | $O_2$ | $CO_2$ | $H_2O$ |
| 0..... | 5 | 1 | 3 | .. | 10 | 1 | 5 | .. |
| 1..... | 4 | 1 | 1 | .. | 15 | 7 | 5 | 4 |
| 2..... | 2 | 2 | 1 | 2 | 9 | 3 | 5 | 2 |
| 3..... | 1 | 1 | .. | 1 | 4 | 1 | 3 | 4 |
| 4..... .. | .. | .. | .. | 1 | 1 | .. | .. | 3 |
| 5..... | .. | .. | .. | 1 | .. | 2 | .. | 1 |
| 6..... | .. | .. | .. | .. | .. | 2 | 1 | 4 |
| 7..... | .. | .. | .. | .. | .. | 1 | .. | .. |
| 8..... | .. | .. | .. | .. | .. | 1 | .. | .. |
| 9..... | .. | .. | .. | .. | .. | 1 | .. | .. |
| 10..... | .. | .. | .. | .. | .. | .. | .. | 1 |
| Total number of experiments or hours..... | 12 | 5 | 5 | 5 | 39 | 19 | 19 | 19 |
| Average error... | 0.9 | 1.6 | 0.6 | 2.2 | 1.2 | 3.2 | 1.6 | 3.7 |
| Total error..... | −0.33 | −1.69 | −0.68 | +3.09 | | | | |

electric and alcohol checks is: heat, — 0.32 per cent., $O_2$ — 1.69 per cent., $CO_2$ — 0.68 per cent. The total error in the water is + 3.09 per cent.

The electric checks show a smaller error in the measurement of calories than the alcohol, since the dissipation of heat is much more uniform. It is difficult to secure an even flow of alcohol to the burner and the larger errors in the oxygen determination are due to irregularities in the flow during the last five minutes of the period. If a slight negative pressure develops within the box toward the end of the period, alcohol is sucked into the burner causing the flame to flare up

and expand the air before the air thermometers record the rise in temperature. This causes an error in the oxygen calculation which, as the tables show, is usually corrected the next hour. With a trained human subject the production of heat and carbon dioxid and the absorption of oxygen are more regular than in the case of an alcohol check and the error presumably not so large. The cause for the negative total error in the measurement of heat, $O_2$ and $CO_2$, is not clear, but one cannot help suspecting that a slight absorption of water by the alcohol and a slight evaporation as the alcohol drops from the bottle into the buret may account for most of the error. In experiments on man there is another factor which reduces an error in the measurement of oxygen or carbon dioxid considerably. In calculating the indirect calorimetry the factor by which the oxygen or carbon dioxid is multiplied changes with the respiratory quotient and it happens that a plus error in measurement of the gas is partially offset by a minus change in the factor. This change reduces the error to an extent varying between one-fifth and three-quarters of its original size, unless the errors in both gases are in the same direction, leaving the quotient unaltered. The accuracy of the calorimeter has also been demonstrated by the close agreement of the methods of direct and indirect calorimetry. This will be taken up in detail in the paper on normal controls, but at this point it may be said that in a total measurement of 4,577 calories the two methods agreed within 0.17 per cent., and that in 26-hourly periods on the normal control most carefully studied, the agreement was within 5 per cent. in seventeen of the hours.

In spite of the fact that some of the errors published in the table are larger than those published in connection with other types of apparatus, we feel justified in believing that the Sage calorimeter is the most accurate and most reliable instrument of its size used in the study of the respiratory metabolism. The table includes all the alcohol and electric checks, good, bad and indifferent, made during the period when the machine was used for experiments. The only ones left out are those made at the beginning of the season while the apparatus was being put in order, and actual work was never begun before obtaining a check good enough to publish. To the best of our knowledge this method of publishing all the tests has never been used in connection with other types of respiration apparatus, and we have no detailed information as to their average, maximum and total errors.

It is to be regretted that we have not been able to make long electric tests to determine the hydrothermal equivalent of the calorimeter. The storage batteries are not powerful enough to furnish current for more than four hours in addition to the preliminary period of 30 to 40 minutes, and we have never felt justified in using the house current

with its variations in voltage. Numerous short tests showed that the hydrothermal equivalent was very close to 19 liters of water, and this figure gave results within 0.3 per cent. in the check of May 11 with a large temperature change in the second hour. Incidentally, the advantage of a wooden frame is shown by the rapidity with which the box responded to this temperature variation.

### DETERMINATION OF WATER ELIMINATION

In all types of respiration apparatus the measurement of the water elimination has presented great difficulties. This was studied in detail by Benedict, Riche and Emmes, who found that long experimental periods were required to obtain accurate results. The interior of the Sage calorimeter is tinned and polished and there is very little wood-work and cloth, but still a considerable amount of moisture can be retained within the box. In alcohol checks with a water production of only 10 to 14 grams an hour the air becomes dryer and dryer, and this moisture is given off during the whole test, making uniformly a plus error. In experiments on normal men the water elimination is about twice this amount and the percentage of moisture changes but little from hour to hour. In patients who have a tendency to sweat, the water given off may amount to 35 to 40 grams an hour, and there is a tendency for the percentage in the air to increase steadily and finally reach the point of saturation. We should expect a plus error in the determination as the air becomes dryer, a minus error as the percentage of moisture increases, and no error while equilibrium is being maintained. After the first hour of an experiment on man it seems fair to expect an error of less than 5 per cent., except in extreme cases of sweating. More accurate results could be obtained only by removing all wood-work, stripping the man naked and increasing the ventilating current. This would involve such artificial conditions that the results would be worthless.

### ADAPTABILITY OF CALORIMETER

By carefully controlling the rate of flow and the temperature of the water in the heat-absorber it is possible to adapt the calorimeter to wide variations in the heat production of the subjects. For example, on April 23, 1914, an experiment was made on a cretin with an average heat production of 26 calories an hour. The next day the subject was a patient with exophthalmic goiter, whose heat production averaged 107 calories. In one case the methods of direct and indirect calorimetry agreed within 0.2 per cent., and in the other within 0.7 per cent. It has also been possible to adapt the calorimeter rapidly to changes in the heat production from hour to hour by changing the temperature of the

ingoing water and in extreme cases by changing the rate of flow at the beginning of a period.

It has been possible in a long series of experiments for two men to take all the readings and make all the calculations in hourly periods. Three men can handle the apparatus with ease during the trying experiments, and most of the alcohol checks, which are much more difficult, have been made with only three in the room. As a rule, the staff arrives shortly before nine o'clock in the morning, makes a three-hour experiment, gets everything in readiness for the next day and leaves the calorimeter room about three or four o'clock in the afternoon. It has been possible, on occasions, to make six experiments in a week. The calorimeter has been very seldom out of commission. Between October 13, 1913, and May 18, 1914, it was possible to make 113 experiments on man and eight alcohol and electric checks.

## SUMMARY AND CONCLUSIONS

The original Atwater-Rosa respiration calorimeter with the improvements added by Benedict, Williams and others has been adapted for clinical study in Bellevue Hospital. The form of the apparatus makes it perfectly comfortable for patients. The accuracy is such that in observations lasting three or four hours the heat production, carbon dioxid elimination and oxygen consumption as determined by alcohol and electric tests can be measured with an average error of 0.9 per cent., 0.6 per cent. and 1.6 per cent., respectively. In periods one hour long the average error for heat measurement was 1.2 per cent., for carbon dioxid 1.6 per cent. and for oxygen 3.2 per cent.

The calorimeter never needs more than three men for its operation, and two men have repeatedly made all the readings and all the calculations in hourly periods.

# CLINICAL CALORIMETRY

THIRD PAPER

## THE ORGANIZATION OF A SMALL METABOLISM WARD*

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All investigators who have attempted to carry on metabolism experiments in hospitals have experienced more or less difficulty in the administration of the diets and the collection of the excreta. The necessity for a special metabolism ward became evident as soon as it was decided to build a respiration calorimeter in Bellevue Hospital. Through the generosity of the trustees of the hospital and the attending staff of the Second Medical Division a small ward holding four or five beds was placed in charge of the medical director of the Russell Sage Institute of Pathology,[1] who was also one of the junior members of the attending staff of the hospital. He is directly responsible to the attending physician for the welfare of the patients, and there has always been a spirit of active cooperation between the small metabolism ward and the large medical wards of the service.

The calorimeter room described in the preceding paper[2] is located on the same floor as the male medical wards of the Second Division in the new Medical Pavilion. The side hall, used as an entrance to the calorimeter room, has been partitioned off to make a small diet kitchen. Next to this is a well lighted ward of four beds used almost exclusively for patients whose metabolism is the subject of active investigation.

The patients are cared for by three graduate nurses, trained in metabolism work and paid by the Institute. The success of the ward is in large measure due to the faithful and intelligent work of the head nurse, Miss Estelle Magill, and her two assistants. They have used the same care in the preparation of food and the collection of excreta that is used in the laboratory and the effort has constantly been made to keep the error within 1 per cent. In order to maintain a high degree of accuracy and at the same time a high standard of nursing it is necessary for the three nurses to devote their whole time to the ward of only four patients. Orderlies, the greatest source of error in metab-

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* From the Russell Sage Institute of Pathology in affiliation with the Second Medical Division of Bellevue Hospital, New York.

1. Dr. Eugene F. DuBois.

2. Riche and Soderstrom: See p. 805.

olism work, are excluded from the ward and patients are never allowed in the hospital dining room or kitchen, and only the most trusted are permitted to leave the room at all. These precautions are necessary in order to afford the certainty that the twenty-four-hour specimens of urine are complete and that the patients have not smuggled in outside food. Patients are not allowed out of sight of the nurse in charge for more than a couple of minutes at a time.

The food supplied to patients in the metabolism ward is all prepared by the special nurses, who have become so skilled in the preparation of the various dishes that they can even make one-sided diets attractive. In fact, the patients enjoy the cooking so much that they are sent to their homes or to the general hospital ward with difficulty. This is a matter of importance when one desires to keep interesting cases under observation. The foods are prepared as often as possible from raw materials whose composition is determined from time to time. Milk and cream have been of fairly constant composition, as the analyses over a period of several years have shown.

By applying some of the principles of business efficiency, the work has been made a great deal easier. The dry cereals, eggs, bacon, etc., are weighed in white enamel dishes and bowls of known weight marked with serial numbers. Milk and cream are measured in measuring cylinders and added to these dishes in which the food is baked, fried or boiled. The dishes with the cooked food are then taken directly to the patient and if by any chance he should leave some of the food it is an easy matter to weigh it back. Egg whites and yolks are weighed separately. Sugars, salt, cocoa, butter, etc., are put up in packages of known weight by the night nurse to save time during the day.

When a patient first enters the ward the nurses spend a couple days in investigating his dietetic limitations and his dislikes, a matter of great importance. A diet such as the following, for example, is then ordered: 3,000 calories, 15 grams nitrogen, ½ non-protein calories in fat, ½ in carbohydrate. The nurses then work out a diet which will fulfil the specifications and at the same time be agreeable to the patient. Often by careful work it is possible to educate a patient to a diet that he could not otherwise tolerate. We cannot too strongly emphasize the need of individualization aided by good cooking in experimental metabolism work.

The method of collecting twenty-four-hour specimens is, we believe, a new one, and since it has proved to be very satisfactory, should be given in detail. A large number of 20-ounce, round, wide-mouthed bottles with cork stoppers are kept in the ward. These have been etched on the side so that one can write on them with a pencil. At 5 a. m., the time at which the twenty-four-hour period ends, each

COMPOSITION OF FOODS USED IN METABOLISM WARD

| Food | Protein | Fat | Carbohydrate | Calories per Gram | 100 Calory Portion |
|---|---|---|---|---|---|
| Beef, chopped | 22.1–48.6 | 2.4–12.8 | 0 | 1.3– 2.0 | 50– 79 |
| Beef broth | 2.1 | 0.2 | 0 | 0.1 | 1000 |
| Bread, white | 9.8 | 0.3 | 53.5 | 2.6 | 38 |
| Chicken, minced | 18.5 | 7.2 | 0 | 1.5– 1.5 | 69 |
| Cabbage, thrice boiled* | ..... | ..... | 0.24 | | |
| Cauliflower, thrice boiled* | 1.75 | ..... | 0.12 | | |
| Cocoa, powdered | 23.1–23.2 | 19.4–25.2 | 48.3–54.0 | 4.8– 5.3 | 19– 21 |
| Cheese, cottage | 14.9–19.2 | 0.2– 1.9 | 0 | 0.6– 0.9 | 118–164 |
| Crackers, soda | 8.3 | 9.3 | 73.2 | 4.3 | 24 |
| Crackers, sugar | 6.2 | 10.7 | 80.1 | 4.5 | 22 |
| Cream | 2.1– 2.9 | 17.1–19.8 | 4.0–5.2 | 1.9–2.1 | 48– 53 |
| Cream | 2.1–2.9 | 17.1–19.8 | 4.0–5.2 | 1.9–2.1 | 48–53 |
| Custard | 5.4 | 3.5 | 21.6 | 1.4 | 70 |
| Custard, hospital diabetic | 5.7 | 5.7 | 7.3 | 1.1 | 94 |
| Farina, dry | 18.9 | 0.9 | 68.2 | 3.7 | 27 |
| Flour, hospital diabetic | 23.2 | 1.3 | 68.2 | 3.9 | 26 |
| Ice cream, vanilla | 3.4– 4.8 | 1.7– 6.9 | 12.2–23.4 | 1.0– 1.6 | 61– 99 |
| Ice cream, chocolate | 3.7 | 5.5 | 12.3 | 1.2 | 85 |
| Jelly, lemon | 2.1 | 0.2 | 17.1 | 0.9 | 111 |
| Junket | 2.1 | 2.1 | 16.6 | 1.0 | 104 |
| Macaroni, dry | 13.7 | 1.2 | 77.5 | 3.9 | 26 |
| Mammala | 26.8 | 9.6 | ..... | 4.2 | 24 |
| Mammala (separated milk) | 31.7 | 5.4 | ..... | 4.0 | 26 |
| Mammala (full cream) | 10.2 | 28.2 | ..... | 5.5 | 18 |
| Milk, hospital | 3.09– 3.1 | 3.3– 4.67 | 4.10– 4.7 | 0.6 | 166 |
| Oatmeal, dry | 15.1 | 5.6 | 71.2 | 4.1 | 24 |
| Potatoes, mashed | 2.2 | 0.2 | 18.0 | 0.9 | 118 |
| Pudding, rice | 4.1 | 3.0 | 24.8 | 1.5 | 68 |
| Pudding, tapioca | 5.7 | 2.3 | 14.8 | 1.1 | 94 |
| Rice, dry | 7.0 | 0.5 | 81.9 | 3.8 | 27 |
| Rice, cooked | 1.4 | 0.3 | 13.1 | 0.6 | 159 |
| Tapioca | ..... | ..... | 91.1 | 3.7 | 27 |
| Special Articles— | | | | | |
| Cane sugar | Sucrose 100 per cent. | | | 3.96 | 25.2 |
| Corn sirup—glucose | Glucose, 41.3 per cent.; dextrin, 33.9 per cent.; sucrose, 2.7 per cent. | | | 3.07 | 32.6 |
| Corn sirup—glucose | Glucose, 42.4 per cent.; dextrin, 44.6 per cent.; sucrose, 0. | | | | |
| Gelatin | ..... | | | | |
| Lactose | Lactose, 98.4 per cent. | | | 37.0 | 27.0 |
| Olive oil | ..... | | | 9.52 | 10.5 |
| Sherry | Alcohol by volume, 19.45 per cent.; Carbohydrate, 1.96 per cent. | | | 1.46 | 68.5c.c. |
| Vinegar | Acetic acid, 4.07 per cent. | | | | |
| Whisky | Alcohol by volume, 41.76 per cent. | | | 2.96 | 33.8c.c. |

* Cooked in three changes of water.

patient is given a bottle and made to empty his bladder. The bottle is then marked with his name, the date, the hour and minute. The volume is estimated for clinical purposes by comparison with a calibrated bottle of the same capacity. The data are then recorded on a special slip of paper to go to the laboratory and also on the diet chart. A little toluene is added to the urine bottle, which is corked and stored in the ice-box along with the previous voidings of that twenty-four-hour period, each voiding being in a separate bottle. At about 9 o'clock in the morning the laboratory man checks up the bottles with the records on the laboratory slip, and with the nurse's notes takes all the bottles to the laboratory, measures the volume accurately, makes up to volume and analyzes a sample.

The only disadvantage of this system is the labor of carrying a number of half-filled bottles, although this is not great if suitable carriers are used. The advantages are as follows: 1. There is no chance of a specimen of urine having been poured into another patient's bottle thus spoiling two twenty-four-hour specimens. 2. If a single voiding is lost the urine for the remainder of the day can be accurately analyzed. 3. The urine can be fractionated and the nitrogen elimination determined in hourly periods, as is frequently done in calorimeter experiments. 4. The bottles make excellent urinals, are less apt to spill than the ordinary ward urinal and are not unsightly even when filled with urine. 5. Since the urines are made up to volume in the laboratory, it is possible to rinse out each bottle with distilled water and collect every drop of urine. 6. The bottles are washed, dried, and, if necessary, sterilized in the laboratory, so that there is no danger of a patient voiding into a urinal containing decomposing urine. 7. The bottles are cheap and can be kept on hand in large numbers, so that the patients need never wait for the urinal. 8. While we have never had occasion to use them in a general ward, there is no reason why they should not be used instead of the common type of expensive and unsightly urinal. In collecting single specimens for the usual routine analysis the nurse could put a bottle by each bed in the morning and send the desired specimens directly to the ward laboratory without transferring to a special jar. It is surprising how long urines will remain clear if voided into and kept in a clean bottle.

The collection of feces is somewhat more difficult. Patients who can get out of bed defecate into a weighed bucket in the commode. This bucket is then weighed again. A little formalin is added and the whole sent to the laboratory where the specimen is thoroughly mixed and one-tenth removed to be dried and added to the other aliquot portions of that period and analyzed. Bed-ridden patients use a weighed bed pan from which the feces are transferred to a covered bucket for

transportation. Most of the patients with acute diseases are given every morning an enema of hypertonic salt solution. Oil and soap enemas of course interfere with the accuracy of the fat analyses; glycerin enemas make it impossible to dry the feces. To divide the periods, powdered carmin (0.3 gm., 5 grains) is given with the first meal of the period and with the first meal after the period is ended. Experience has shown that it is much easier to determine the exact point of appearance of the carmin in the feces than to find the point of disappearance. When patients are being given enemas it is easier to discover traces of carmin than traces of charcoal. Periods are made as long as possible to minimize the errors of division.

A special diet sheet has been provided by the hospital on which the nurses record the weights of raw material given to the patient and make the calculations from the table of known composition of the food. On this sheet is a summary column giving carbohydrate, fat and protein grams and calories, total calories, nitrogen of the food, of the urine, of the total excreta and the nitrogen balance; weight of the patient and food calories per kilogram. In another place are columns for recording the time and amount of each voiding and each defecation.

Patients are weighed at 9.00 a. m. every day or every other day on a "silk scale" accurate to 10 grams. Bed patients are weighed on a platform resting on these scales in the manner described by Coleman.[3] The nurse slides the patient on the smooth platform which is just at the level of the bed, weighs him and then makes up the bed while he is still on the balance. The whole procedure has been found to be a convenience for the nurse rather than a time-consuming task.

Nitrogen determinations are made by the Kjeldahl method, ammonia, uric acid, creatin, creatinin, and indican by Folin's[4] methods, urea and glucose by the methods of Stanley R. Benedict.[5]

The calorific value of the foods has been determined by means of the Riche[6] bomb calorimeter. Food fat analyses have been made in a Soxhlet apparatus. Carbohydrates were determined by a difference using in the later work a new procedure described by Gephart.[7] The

3. Coleman: Diet in Typhoid Fever: Journal Am. Med. Assn., 1909, liii, 1145.

4. Folin: Approximately Complete Analysis of Thirty Normal Urines, Am. Jour. Physiol., 1905, xiii, 45.

5. Benedict: The Detection and Estimation of Glucose in Urine, Jour. Am. Med. Assn., 1911, lvii, 1193. The Estimation of Urea in Urine, Jour. Biol. Chem., 1910, viii, 405.

6. Riche: An Improved Type of Calorimeter for use with any Calorimetric Bomb, Jour. Am. Chem. Soc., 1913, xxxv, 1747.

7. Gephart, Frank C., and Csonka: In the Estimation of Fat in Feces, Jour. Biol. Chem., 1914, xix, 521.

dried feces were powdered and the fat determined at first by the Kumagawa-Suto method and later by the new saponification procedure described by Gephart.[8] In calculating food values, Rubner's factors were used, namely: for fat 9.3 calories; for carbohydrate and protein, 4.1 calories per gram.

8. Kumagawa and Suto: Ein neues Verfahren zur quantitativen Bestimmungen des Fettes und der unverseifbaren Substanzen in tierschen Material nebst der Kritik einiger gebrauschlischen Material, Biochem, Ztschr., 1908, viii, 212.

# CLINICAL CALORIMETRY

FOURTH PAPER

## THE DETERMINATION OF THE BASAL METABOLISM OF NORMAL MEN AND THE EFFECT OF FOOD*

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The importance of the normal control has been emphasized so strongly by the serologists and the management of the control has been developed by them to such an art that it has seemed advisable to apply some of their methods of critique to the study of the respiratory metabolism. Serologists insist that a man shall make his own controls with the same apparatus and exactly the same technic as in the experiments and they also insist that the controls shall be numerous enough to show individual variations in their true proportions. These precautions and many others have been made necessary by the fact that the normal control is usually the point of attack in serological controversies. Likewise in the study of metabolism the normal control is coming to be recognized as the weakest part of the experiment. The chemical methods of blanks and duplicates will not suffice; the living organism is the uncertain factor. The literature is notoriously filled with false theories, of which by far the greater part would never have been promulgated if sufficient attention had been given to normal controls.

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* From the Russell Sage Institute of Pathology, in affiliation with the Second Medical Division of Bellevue Hospital.

† With the technical assistance of G. F. Soderstrom and R. H. Harries.

The three papers immediately preceding have described the Sage respiration calorimeter in Bellevue Hospital and its adjoining metabolism ward. Before presenting any of the work in pathological conditions it has seemed best to study in detail the results obtained on the normal controls. It was the original intention to use a large number of normal subjects and determine the individual variations in metabolism, but this laborious piece of work was gladly abandoned when it was learned that Benedict and his collaborators were engaged in the task. In pathological conditions the work has been confined as much as possible to men between the ages of 20 and 50 who do not depart very markedly from the normal relationship between height and weight. Consequently the normal controls have been selected to comply with these requirements.

## BASAL METABOLISM

As a basis of comparisons between all normal individuals and groups of patients the heat production in the morning from fourteen to eighteen hours after the last meal with the individual at complete rest, was selected. This has been termed the *"nüchtern"* metabolism by the Germans, the "post-absorptive" by Benedict and Cathcart,[1] but the simplest and most satisfactory term is "basal metabolism," a translation of the German *Grundumsatz,* as used by Lusk and his coworkers[2] in the series of papers published under the heading of Animal Calorimetry.

The literature of the respiratory metabolism of healthy men has been admirably reviewed by Benedict and Carpenter[3] in 1910 and Loewy[4] in 1911. In the former monograph the results of a large number of experiments with the respiration calorimeter of Wesleyan University are gathered in numerous tables. During the so-called rest experiments, however, the subjects were allowed to move about the room and indulge in minor muscular activities, something which had

1. Benedict and Cathcart: Muscular Work, Carnegie Institution of Washington, 1913, Pub. 187.

2. Lusk: Calorimetric Observations, Med. Rec., New York, 1912, lxxxii, 925; Williams, Riche and Lusk: Animal Calorimetry, Second Paper. Metabolism of the Dog Following the Ingestion of Meat in Large Quantity, Jour. Biol. Chem., 1912, xii, 349; Lusk: Third Paper, Metabolism After the Ingestion of Dextrose and Fat, Including the Behavior of Water, Urea and Sodium Chlorid Solutions, Ibid., 1912, xiii, 27; Lusk: Fifth Paper, The Influence of the Ingestion of Amino-Acids upon Metabolism, Ibid., 1912, xiii, 155; Lusk: Sixth Paper, The Influence of Mixtures of Foodstuffs Upon Metabolism, Ibid., 1912, xiii, 185.

3. Benedict and Carpenter: The Metabolism and Energy Transformations of Healthy Man During Rest, Carnegie Institution of Washington, 1910, Pub. 126.

4. Loewy: Oppenheimer's Handbuch der Biochemie der Menschen und der Thiere, Jena, 1908, iv,[1] 172.

been permitted in practically all the large respiration chambers. Benedict and Carpenter measured the increased heat production caused by certain simple movements which their subjects had performed during the experiments. The act of rising from a chair, taking one or two steps, opening the food aperture, removing the food, closing the window and returning to the chair required only 19 to 29 seconds, but involved the expenditure of 1.22 calories. Considering the short time involved in the operation, the heat production was increased from 200 to 300 per cent. They also found the metabolism 15 per cent higher when the subject was standing than when he was sitting, and from 8 to 10 per cent. higher when lying awake than when sleeping. The sleeping periods were between 1 a. m. and 7 a. m., and the waking periods followed immediately in the three experiments which were really satisfactory. During the waking periods there was an increase in the oxygen consumption amounting to 1.7, 0.9 and 11.5 per cent., while the heat production was increased 5.8, 15.2 and 13.1 per cent. Some of this increase may be accounted for by difference in the time of day, some by small muscular movements. Johansson[5] found that with complete muscular relaxation the carbon dioxid production was the same as during sleep. The two individuals (H. C. K. and H. R. D.) studied by Benedict and Carpenter produced during sleep 35.2 and 36.2 calories per square meter of body surface, whereas only three of the twelve normal men, whose metabolism is recorded in Table 3, produced more than 35.1 calories per square meter per hour. It is obvious that if the metabolism of H. C. K. and H. R. D. were increased 5.8 per cent., 15.2 per cent. and 13.1 per cent., this increase would carry them just so much farther into the zone where it is necessary to assume muscular activity to account for the abnormally high metabolism.

In anticipation it may be well to mention that the average basal heat production of the individuals we are reporting is 34.7 calories per square meter per hour, the subjects lying awake, at perfect rest during the morning hours. The average heat production of the nineteen subjects of Benedict and Carpenter while asleep between the hours of 1 a. m. and 7 a. m. was 35.3 calories and of fifty-five individuals while awake and moving from time to time in the calorimeter was 49.2 calories per square meter per hour. The fact that their sleeping subjects showed a metabolism 3 per cent. higher than our subjects awake may substantiate the conclusions of Johansson. Benedict and Carpenter pointed out at the conclusion of their monograph (p. 246) the fact that the figure 49.2 calories per square meter per hour, equaling

5. Johansson: Ueber die Tageschwankungen des Stoffwechsels und der Körpertemperatur in nüchternem Zustande und vollsändige Muskelruhe, Skand. Arch. f. Physiol., 1898, viii, 85.

36.5 calories per kilogram per day, represented not the condition of true rest, but rather that of a person confined for the day to a small room but allowed to dress and undress, sit in a chair, feed himself, etc.

Since the appearance of this monograph Benedict and his coworkers, and also other investigators, have insisted more and more strongly on the necessity of absolute quiet in rest experiments and as a check on muscular activity a graphic record of all movements. This eliminates for our purposes practically all the work done in large respiration chambers before 1910 and leaves us only the work done by means of the small types of apparatus, and especially the Zuntz-Geppert apparatus, by Magnus-Levy and Falk,[6] and by Loewy. The results of the determinations on nineteen normal individuals have been collected in a table by Loewy[7] which is reprinted by Benedict and Joslin.[8] Coleman and DuBois,[9] in gathering normal controls to compare with their typhoid patients, grouped these cases of Loewy with twenty-seven normal controls taken from the work of Benedict and Joslin, and with two of their own cases. The average heat production of the total forty-eight normal men was 33.7 calories per square meter of body surface per hour. Very recently Benedict, Emmes, Roth and Smith[10] published a brief report of their important work on the basal metabolism of a total of eighty-nine men and sixty-eight women. The early appearance of these determinations has been of great service to us, and we wish to express our appreciation to these investigators for the publication of the most essential part of their data.* All their determinations were made on healthy subjects in the morning at least twelve hours after the last meal, with the subject at complete rest. Some of the experiments were made in the bed calorimeter of the Nutrition Laboratory of Boston, but most of them were short experiments made with the small Benedict "universal respiration apparatus." The fact that this small machine gives results almost identical with the calorimeter was amply proved by Benedict[8] and his coworkers and confirmed by the limited amount of work done with both types of apparatus by

6. Magnus-Levy and Falk: Der Lungengaswechsel des Menschen in verschiedenen Alterstufen, Arch. f. Anat. u. Physiol., 1899, Supp. 314.

7. Loewy: Oppenheimer's Hand. der Biochemie der Menschen und der Thiere, Jena, 1908, iv,[1] 179.

8. Benedict and Joslin: Metabolism in Diabetes Mellitus, Carnegie Institution of Washington, 1910, Pub. 136; A Study of Metabolism in Severe Diabetes, ibid., 1912, No. 176. Ueber der Stoff- und Energieumsatz bei Diabetes, Deutsch. Arch. f. klin. Med., 1913, cxi, 333.

9. Coleman and DuBois: The Influence of the High Calory Diet on the Respiratory Exchanges in Typhoid Fever, THE ARCHIVES INT. MED., 1914, xiv, 168.

10. Benedict, Emmes, Roth and Smith: The Basal, Gaseous Metabolism of Normal Men and Women, Jour. Biol. Chem., 1914, xviii, 139.

*A more complete discussion of the work is appearing in the Jour. Biol. Chem., March, 1915.

Coleman and Du Bois.[9] The average heat production of the eighty-nine men was 34.7 calories per square meter per hour, and of the sixty-eight women, 32.2 calories. The lower heat production of women is in accord with the previous findings of Sonden and Tigerstedt.[11]

The work of Magnus-Levy and Falk[6] showing the diminution of metabolism in old age and the increase in youth is also confirmed. The two men over 50 years of age produced only 28.9 calories per square meter. The eight youths between 17 and 20 averaged 37.1 calories, nine who were 20 years old, 36.6 calories, seven who were 21 years old, 36.1 calories.

### SPECIFIC DYNAMIC ACTION OF FOODS

The subject of the specific dynamic action of foods in increasing metabolism is fully discussed by Lusk[12] in his text-book and in a series of papers on animal calorimetry.[2, 13]

From his work on dogs, Lusk has concluded that the specific dynamic action of protein is due to the stimulation of the metabolism of the cells by certain of the amino-acids while the action of fat and carbohydrates is due to the mass action of these metabolites in the circulation. He has found marked differences in the action of the various amino-acids and the various carbohydrates. The study of the specific dynamic action of foods on man is not nearly as far advanced as in the case of the dog. Magnus-Levy[14] in connection with his work on dogs found that after giving a man 50 to 60 grams of carbohydrate the metabolism was increased in the first hour from 2 to 12 per cent., in the second hour 0 to 7 per cent. After 140 to 160 grams of starch in bread the increase in the first hour averaged 22 per cent., the second hour 14 per cent., the third hour 16 per cent. After 210 grams of bacon and butter the metabolism was increased 5 to 10 per cent. for seven to eight hours, while after 210 to 250 grams of beef the oxygen consumption rose from 3 to 12 per cent. the first hour and then 15 to 34 per cent. in the next six hours. Gigon[15] obtained similar results using a Jacquet apparatus. In the period of four to five hours following the ingestion of 100 grams of dextrose there was an increase of 9.5 per cent. in the oxygen consumption. After 50 grams of casein the oxygen was increased 5.5 per cent. and after 100 grams 16.8 per cent.

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11. Sonden and Tigerstedt: Untersuchungen über die Respiration und den Gesammtestoffwechsel des Menschen, Skand. Arch. f. Physiol., 1895, vi, 99.
12. Lusk: The Science of Nutrition, Philadelphia, 1909, second edition; Stoffwechsel und Ernährung; Deutsche Uebersetzung von L. Hess, 1910.
13. Lusk: The Cause of the Specific Dynamic Action of Protein, THE ARCHIVES INT. MED., 1913, xxi, 485.
14. Magnus-Levy: Ueber die Grosse des respiratorische Gaswechsels unter dem Einfluss der Nährungsaufnahme, Arch. f. d. ges. Physiol. (Pflüger's), 1894, lv, 1.
15. Gigon: Ueber den Einfluss der Nährungsaufnahme auf den Gaswechsel und Energieumsatz, Arch. f. d. ges. Physiol. (Pflüger's), 1911, cxl, 509.

EXPERIMENTAL PROCEDURE

The normal controls who were kept in the metabolism ward were given a maintenance ration, the last meal of the day being about 5 p. m. At 5 a. m. they were awakened, given an enema, and instead of breakfast, a cup of coffee without cream or sugar. At about half past nine the calorimeter bed was wheeled to the ward on the weighing platform, which is provided with large casters, and the subject lifted from his bed, weighed, rolled back to the calorimeter room and slid into the calorimeter, bed and all. He was dressed in a night shirt, thick ward pajamas and thick socks, and, as a rule, the legs were covered with a sheet, although some subjects needed a thin blanket and others required no covering. A soft pillow was placed under the head and sometimes one under the knees. Every effort was made to ensure absolute comfort, a matter of great importance in work on the respiratory metabolism.

Those normal controls who lived at home took their evening meal at 6 or 7 o'clock, rose at 6 or 7 a. m., drank a cup of black coffee, took the street car, walked about ¼ mile and arrived at the hospital at 9 o'clock. They then undressed, weighed themselves, dressed in warm pajamas and entered the calorimeter.

As soon as the subject was in the calorimeter the rectal thermometer was inserted about 12 cm. in the rectum, giving slight discomfort for a few minutes, but later remaining in position without the man's being conscious of its presence. The surface thermometers were next fastened tightly to the thorax, axillae or abdomen by means of adhesive plaster and the whole covered with a pad of absorbent cotton about 20 cm. in diameter and 3 or 4 cm. thick, this being held in place by strips of adhesive. The Bowles stethoscope was next strapped over the apex of the heart and the whole covered with night shirt and pajamas. When this was finished the bed was shoved all the way into the box, the ventilation started, and at about a quarter past 10 the glass plates were sealed in the end of the calorimeter and the heavy front put in position, making it possible to start the preliminary period shortly after half past ten.

The actual preparation of the calorimeter had begun long before this. On the previous afternoon all sulphuric bottles, soda-lime containers, etc., had been filled and the oxygen tank weighed so that any leakage over night might be detected. The temperature of the calorimeter room had been watched every hour by the night nurse and maintained within 1 degree of the standard experimental temperature of 23 C. At nine in the morning the water circulation through the various cooling coils and the absorber had been started and a lighted 32 candle power electric lamp placed in the box until the subject was ready. If

these precautions had been carefully followed and if the observer had watched the temperature of the various parts of the apparatus, it was possible to bring the box into perfect equilibrium and control fifteen to twenty minutes after the start of the preliminary period. As we shall see later, there is reason to believe that during the first hour after the box is sealed the wooden frame of the bed may absorb a little heat owing to its proximity to the subject's body.

As a rule the preliminary period lasts thirty to forty minutes and the experiment begins shortly after 11 o'clock. Eight minutes before the start a sign is hung in the window telling the subject to remain absolutely quiet and the first residual sample of ten liters of air is drawn through U tubes by means of the Bohr meter. At four or five minutes before the start the second residual is begun and a tracing of the spirometer curve made in the manner first used by Benedict and Carpenter. At "time" the various cocks and switches are turned

TABLE 1.—THE STATISTICS OF THE NORMAL CONTROLS

| Subject | Weight, Kg. | Height, Cm. | Chest Circumference, Cm. | Age, Yrs. |
|---|---|---|---|---|
| G. L. | 78.4 | 175.5 | 90.5 | 47 |
| E. F. D. B. | 73.6<br>75.5 | 178.8 | 91.5 | 31-32 |
| F. C. G. | 56.5 | 173.9 | 80.2 | 29 |
| R. H. H. | 62.0 | 177.2 | 85.3 | 21 |
| L. C. M. | 50.5 | 170.6 | 86.6 | 22 |
| Louis M. | 51.7 | ..... | .... | 27 |
| John L. | 70.9 | ..... | .... | 44 |

as described in the previous article. One or two minutes after "time" the subject is allowed to shift his position, and, if necessary, void into a tared urine bottle which he then places on a small spring balance so that the exact weight of urine passed can be read through the calorimeter window. During the remainder of the hour he lies as quiet as possible trying not to turn from back to side and vice versa more than once an hour. The work-adder on the spirometer records each movement and the electrical control of the calorimeter is so delicate that the observer in charge of the thermometers can detect such slight activity as turning the head to look out of the window by the rise in the temperature of the air and wall. At the close of the first and subsequent hours the procedure is the same as at the start, except that only one sample of residual air is analyzed.

The statistics of the normal controls are as shown in the accompanying table (Table 1).

DESCRIPTION OF SUBJECTS AND DETAILS OF EXPERIMENTS

G. L., physiologist, large frame, slightly adipose. Has taken but little exercise during the last few years. Health good, no recent illnesses. Physical examination negative.

*Experiment 1.*—March 11, 1913. Although this was the first experiment on man made with the Sage calorimeter, the accuracy of the machine had been thoroughly tested by means of the alcohol checks described in Paper 2. The temperature of the air in the calorimeter was 24.5 C. in this experiment instead of the temperature of 23 C. used later. In addition to a suit of pajamas, the subject wore a heavy sweater. The basal metabolism was determined in the first two hours and at the beginning of the third hour he drank a solution of 115 grams commercial glucose (dextrose 42.37 per cent., dextrin 44.57 per cent., water 13.50 per cent.) in 500 c.c. water and 10 c.c. lemon juice. The commercial glucose was equivalent in calories to 100 grams dextrose. The subject, who had felt somewhat too warm during the first two hours, perspired profusely after the glucose. He remained very quiet during the five hours.

E. F. D. B., physician, large frame, moderate adipose. Up to the age of 22 in good athletic condition; since then has exercised in steadily decreasing amounts. During the winter of 1913 took violent exercise for about half an hour twice a week; in 1914 scarcely exercised at all. General health good; no recent illnesses. Heart, lungs, etc., normal.

*Experiment 2.*—March 13, 1913. The basal metabolism was determined in the first two hours, and at the beginning of the third hour he drank 115 grams commercial glucose in the same solution as in the experiment on G. L. The temperature of the calorimeter was 22 C. and his clothing consisted of thin undershirt and pajamas. He did not perspire but blew his nose several times each hour, spent a good deal of the time looking out of the window and was distinctly more restless than in the subsequent observations.

*Experiment 25.*—May 17, 1913. Basal determination only. Was very quiet during all three hours and dozed from 11:30 to 11:50.

*Experiment 27.*—May 22, 1913. At 8:55 a. m., before entering the calorimeter, drank 230 gm. commercial glucose (equivalent to 200 gm. dextrose) in 500 c.c. water and 15 c.c. lemon juice. Six minutes were required to drink the mixture. Dozed at times during the experiment.

*Experiment 115.*—March 30, 1914. Basal metabolism only. This experiment was conducted by only two observers, Mr. Soderstrom and Mr. Harries, and the periods were made one and one-half hours long to give them more time for weighings, etc. In the subsequent experiments on this subject these two observers alone were able to make all measurements and keep up with the calculations in hourly periods, a record of which they may well be proud, especially since the agreement between the direct and indirect calorimetry was unusually good.

*Experiment 116.*—April 1, 1914. Just before entering the calorimeter between 9:45 and 10:07 a. m., the subject ate the following meal containing 10.5 gm. nitrogen: fat-free milk, 600; pot cheese (cottage cheese or *Schmierkäse*), 150; egg-white, 120; egg-yolk, 20. During this experiment the work-adder was out of order and recorded part of the excursions of the spirometer due to the admission of oxygen to the box. The subject was very quiet, much more quiet than the work-adder record would indicate.

*Experiment 138.*—May 8, 1914. Between 10:05 and 10:07 a. m., drank a solution of 200 gm. C. P. Dextrose (Merck) in 400 c.c. water and 35 c.c. lemon juice. No glycosuria resulted in this or any other of the experiments on normal controls.

*Experiment 141.*—May 15, 1914. An attempt was made to raise the respiratory quotient as high as possible by filling the glycogen stores of the body

before giving the dextrose. At 11:30 the night before the experiment and again at 6:15 in the morning the subject ate the following carbohydate meal: shredded wheat, 55 gm.; milk, 100 c.c.; cane sugar, 10 gm.; in the morning taking an additional 10 gm. cane sugar in coffee. Between 9:50 and 9:53 he drank a solution of 200 gm. C. P. Dextrose in 400 c.c. water and 35 c.c. lemon juice.

F. C. G., chemist, thin. At age of 16 had an attack of malaria lasting two weeks. Has not been sick in bed since then and has never weighed over 64 kg. (140 pounds). Has never taken systematic exercise, except baseball from 1900 to 1906. Appetite fair, sleeps well. Physical examination: complexion pale and somewhat sallow; hemoglobin normal; state of nutrition rather poor; heart, lungs and abdomen normal. Experiment 142, May 18, 1914. Basal determination.

*Experiment 3.*—March 17, 1913. The basal metabolism was determined between 9:02 and 12:02, the subject going into a profound sleep in the second and third hours. The calorimeter was then opened and the subject ate the *Haferschleim* mixture of Schmidt's test diet. This contained 40 gm. dry oatmeal, 10 butter, 200 milk and one egg, or approximately, protein, 13.1, fat, 10.2, carbohydrate, 35.5 gm. At the end of the observation it was apparent that the respiratory quotients were abnormally low and that the apparent oxygen consumption was much higher than was consistent with the direct calorimetry. The cause for this was found in a leak in the oxygen cylinder, making it necessary to omit the oxygen figures from the data and base the calculations on the direct calorimetry alone.

*Experiment 17.*—April 22, 1914. Basal determination. The subject remained very quiet, but took care not to go to sleep. Unfortunately the oxygen cylinder leaked again and the calculation of the indirect calorimetry was not accurate.

R. H. H., chemist, tall and spare with long and rather thin bones, very little adipose. At the age of 12 had pneumonia, since then always well. Up to four years ago played semiprofessional baseball or basketball almost every day. Since 1910 his exercise has been limited to four to ten miles of walking a day and in summer a swim of about two miles a day. Physical condition good, heart, lungs and abdomen normal.

*Experiment 4.*—March 13, 1913. Basal determination. During the experiment this subject tried to void at the beginning of each hour but was unable to do so and was slightly more nervous and more active than the other subjects. He could not void before his first meal after the experiment and it has therefore been necessary to omit the figures for the urinary nitrogen and base the calculations on the tables of Magnus-Levy,[16] assuming that 15 per cent. of the calories were derived from protein.

Louis M., barber, small frame, short and thin, muscles fairly firm. This subject was in the hospital from September 7 to October 30, 1912, with a moderately severe attack of typhoid fever, and served as a subject of numerous observations by means of the Benedict universal respiration apparatus (Coleman and DuBois[9]). He was born in Germany and came to New Orleans in 1911. There he suffered from a severe attack of malaria but has had no recurrences. His family history shows that one sister is insane.

After his attack of typhoid he left the hospital in excellent condition and he has been perfectly well for the last four months, although at first he was somewhat weak and easily tired. Physical examination shows heart, lungs, abdomen, etc., to be normal.

*Experiment 7.*—March 26, 1913. Basal metabolism. Subject remained in the metabolism ward four days. On the evening previous to this experiment

16. Magnus-Levy: Von Noorden's Handbuch der Pathologie des Stoffwechsels, Ed. 2, 1906.

at 5 p. m., ate a dinner containing protein, 35.1 gm., fat, 37.1, carbohydrate, 105.6. During the experiment he lay very quiet, dozing most of the time.

*Experiment 8.*—March 28, 1913. March 27 his food contained protein, 80.6; fat, 168.9; carbohydrate, 268.7 gm.; the last meal of the day at 6 p. m. containing protein, 28.9; fat, 61.7; carbohydrate, 82.3 gm. Just before entering the box, between 8:25 and 9:25 a. m., he ate 725 gm. chopped beef, fried in butter, the whole containing 23.93 gm. nitrogen and 100 gm. fat. During the experiment he slept from 12:26 to 1:18 p. m. and from 3:22 to 3:30. There was a small leak from the absorber pipe into the calorimeter, making the apparent water elimination about 1 gram an hour too high.

John L., dentist, medium frame, medium height, well nourished, muscles flabby. This subject, who was born in Sweden, served as a normal control in the metabolism experiments of Dr. R. A. Cooke,[17] who investigated the functional powers of the kidneys. Careful tests showed in this subject a slight delay in the excretion of sodium chlorid, but there were no other signs of kidney disease. He gave a history of moderate indulgence in alcohol. In 1904 he was jaundiced; a few months prior to the experiment he suffered from an infected hand after a dog bite. For the last five years he has been nervous. He was admitted to the hospital Jan. 15, 1914, suffering from a few small boils and a pedicular eruption. His ailments were so slight that he was induced to remain in the hospital as a normal control and, being without a home, he was glad to remain. Physical examination showed a thorax with flaring ribs and an increased anteroposterior diameter of the chest with hyperresonant percussion note and breath sounds somewhat distant. The teeth were in poor condition; blood-pressure, systolic 115 to 130, diastolic 75 to 90.

*Experiment 113.*—March 26, 1914. Basal metabolism. During the previous day the diet had contained 11.5 gm. KCl and a minimum of NaCl. The last meal at 6 p. m. had consisted of farina, 25; egg-white, 50; yolk, 50; sugar, 50; cream (20 per cent. fat), 60; KCl, 3.5 gm. Blood-pressure March 25, systolic, 140; diastolic, 95; just before the calorimeter experiment, systolic 135, diastolic 105.

L. C. M., laboratory helper, small frame, somewhat short and thin. He was born in Sicily where he lived until the age of 11. Shortly before leaving for this country he suffered from malaria, but since then has been in good health. For the last five years he has worked in the daytime and gone to school at night, consequently has taken but little exercise. Heart, lungs and abdomen normal.

*Experiment 136.*—May 4, 1914. Basal metabolism.

*Experiment 137.*—May 6, 1914. Between 9:50 and 9:53 drank a solution of 200 gm. C. P. dextrose in 400 c.c. water and 35 c.c. lemon juice. No glycosuria.

The subjects have been described in detail above and particular attention has been given to the athletic history, since the recent work in Benedict's laboratory (personal communication) has shown a difference in the metabolism of athletes and non-athletic individuals. From a study of the results in previous determinations of the normal metabolism one is led to suspect that a few distinctly abnormal cases have crept in. It has, therefore, been our practice to give the normal controls as careful physical examination as the patients. The importance of this is manifest if one considers that the onset of hyperthyroidism is usually accompanied by the symptoms of exuberant good health.

17. Cooke: Unpublished.

The details of the individual experiments are given below. The body weight at the start of the experiment is determined by weighing the subject shortly before he enters the calorimeter and then making the proper corrections for food, urine and insensible perspiration. All calculations are made from this weight, the surface area being reckoned from Meeh's[18] formula $12.312 \sqrt[2]{WT^2}$. Some actual determinations of the surface area of E. F. D. B. have shown that Meeh's formula is 14.3 per cent. too high in his case, while it is only 7.3 per cent. too high in the case of R. H. H. Calculated from a new formula, Meeh's figures are 14.5 per cent. too high in the case of G. L., 9.3 per cent. too high in the case F. C. G. and 13.4 per cent. too high in the case of L. C. M. These measurements will be given in detail in a subsequent paper. For purposes of uniformity, however, calculations are based on Meeh's formula, since this has been used in all other metabolism work. The work-adder was not attached to the calorimeter until May 16, 1913, and an exact record of the activity of the subjects was not obtained before this date. After the work-adder as described in Paper 2 was attached it was possible to compare the activity in different periods and in different experiments and express this in terms of the number of centimeters that the plummet was raised by the expansion of air within the box. The excursion of the plummet for certain movements of the subject was roughly calculated as follows: Raising arm to head, 0.3 cm.; lifting telephone to mouth, 4 cm.; turning from back to side, 7 cm.

In the tables the final calculations of calories per hour have been based on the indirect calorimetry as calculated from the oxygen consumption and the respiratory quotient. In the two experiments on F. C. G., where these were inaccurate the direct calorimetry was used, and in one of the hours in the experiment on G. L. where the $CO_2$ measurement was lost the non-protein R. Q. for the purposes of calculation was assumed to be 1.00.

In the experiments on E. F. D. B. on May 22 there was an evident error in the division of oxygen between the second and third and the fourth and fifth periods, so these were averaged in the final calculations

The methods of calculation have been described in Paper 1, but it may be well to remind the reader that the method of direct calorimetry represents the heat eliminated from the body, plus or minus the heat stored in or lost from the body, when the temperature of the body rises or falls. The calculation of the percentage of calories derived from protein, fat and carbohydrate is based on the urinary nitrogen and the non-protein respiratory quotient.

18. Meeh: Oberflächenmessungen des menschlichen Körpers, Ztschr. f. Biol., 1879, xv, 425.

TABLE 2.—EXPERIMENTAL—

| Subject Date | Weight Kg. | Period | End of Period | $CO_2$, Gm. | $O_2$ Gm. | R. Q. | $H_2O$, Gm. | Urine N Per Hour, Gm. | Indirect Calorimetry, Cal. | Heat Eliminated, Cal. |
|---|---|---|---|---|---|---|---|---|---|---|
| G. L. ..... 3/11/13 | 78.42 | Preliminary | A. M. 9:50 | | | | | | | |
| | | 1st Hr. ..... | 10:50 | 25.26 | 21.51 | 0.85 | 37.03 | 0.487 | 72.35 | 76.77 |
| | | 2d Hr. ..... | 11:50 | 26.56 | 25.90 | 0.75 | 37.84 | 0.487 | 84.85 | 86.10 |
| | | 1st Hr. P. C. | P. M. 12:50 | 29.61 | 28.57 | 0.75 | 37.88 | 0.404 | 94.12 | 87.75 |
| | | 2d Hr. P. C. | 1:50 | ..... | 25.75 | .... | 39.24 | 0.404 | 86.76* | 92.53 |
| | | 3d Hr. P. C. | 2:50 | 30.33 | 23.44 | 0.94 | 38.98 | 0.404 | 80.86 | 95.67 |
| E. F. D. B. 3/13/13 | 73.6 | Preliminary | A. M. 9:35 | | | | | | | |
| | | 1st Hr. .... | 10:35 | 27.22 | 25.27 | 0.78 | 27.91 | 0.554 | 83.52 | 77.85 |
| | | 2d Hr. ..... | 11:35 | 25.28 | 21.32 | 0.86 | 26.53 | 0.554 | 71.75 | 71.94 |
| | | 1st Hr. P. C. | P. M. 12:35 | 29.51 | 23.58 | 0.91 | 31.19 | 0.621 | 80.27 | 84.87 |
| | | 2d Hr. P. C. | 1:35 | 31.12 | 25.50 | 0.89 | 30.50 | 0.621 | 86.42 | 82.87 |
| | | 3d Hr. P. C. | 2:35 | 30.30 | 24.94 | 0.88 | 30.40 | 0.621 | 84.41 | 81.46 |
| | | 4th Hr. P. C. | 3:35 | 29.92 | 24.10 | 0.90 | 32.02 | 0.621 | 81.92 | 86.02 |
| E. F. D. B. 5/17/13 | 75.51 | Preliminary | A. M. 9:30 | | | | | | | |
| | | 1st Hr. ..... | 10:30 | 25.41 | 22.37 | 0.83 | 34.22 | 0.526 | 74.69 | 76.83 |
| | | 2d Hr. ..... | 11:30 | 25.45 | 21.95 | 0.84 | 32.00 | 0.526 | 73.60 | 76.67 |
| | | 3d Hr. ..... | P. M. 12:30 | 25.00 | 21.24 | 0.86 | 30.68 | 0.526 | 71.41 | 74.13 |
| E. F. D. B. 5/22/13 | 76.10 | Preliminary | A. M. 9:30 | | | | | | | |
| | | 2d Hr. P. C. | 19:30 | 31.13 | 23.04 | 0.98 | 36.24 | 0.581 | 79.77 | 84.61 |
| | | 3d Hr. P. C. | 11:30 | 31.53 | 25.29 | 0.97 | 36.13 | 0.581 | 165.30 | 83.21 |
| | | 4th Hr. P. C. | P. M. 12:30 | 32.45 | 22.49 | | 35.07 | 0.581 | | 83.91 |
| | | 5th Hr. P. C. | 1:30 | 31.95 | 28.84 | 0.95 | 36.63 | 0.581 | 162.04 | 84.45 |
| | | 6th Hr. P. C. | 2:30 | 29.73 | 18.18 | | 36.78 | 0.581 | | 84.96 |
| E. F. D. B. 3/30/14 | 74.34 | Preliminary | A. M. 11:25 | | | | | | | |
| | | 1½ Hrs. .... | P. M. 12:55 | 36.10 | 32.26 | 0.81 | 45.08 | 0.518 | 107.30 | 113.12 |
| | | 1½ Hrs. .... | 2:25 | 37.58 | 34.88 | 0.78 | 46.48 | 0.518 | 115.24 | 113.14 |
| E. F. D. B. 4/1/14 | 74.92 | Preliminary | A. M. 11:27 | | | | | | | |
| | | 2d Hr. P. C. | P. M. 12:27 | 27.47 | 24.30 | 0.82 | 30.51 | 0.856 | 80.50 | 81.65 |
| | | 3d Hr. P. C. | 1:27 | 29.66 | 26.17 | 0.83 | 31.75 | 0.830 | 86.91 | 81.50 |
| | | 4th Hr. P. C. | 2:27 | 28.13 | 25.35 | 0.81 | 32.87 | 0.900 | 83.60 | 85.98 |
| | | 5th Hr. P. C. | 3:27 | 28.83 | 25.89 | 0.81 | 33.39 | 0.577 | 86.11 | 82.75 |
| | | 6th Hr. P. C. | 4:27 | 27.12 | 23.86 | 0.83 | 32.98 | 0.577 | 79.61 | 83.63 |
| E. F. D. B. 5/8/14 | 74.75 | Preliminary | A. M. 11:05 | | | | | | | |
| | | 2d Hr. P. C. | P. M. 12:05 | 30.55 | 23.41 | 0.95 | 32.59 | 0.604 | 80.53 | 76.35 |
| | | 3d Hr. P. C. | 1:05 | 30.91 | 24.28 | 0.93 | 33.55 | 0.604 | 83.08 | 79.08 |
| | | 4th Hr. P. C. | 2:05 | 29.37 | 22.49 | 0.95 | 32.48 | 0.604 | 77.33 | 75.63 |
| | | 5th Hr. P. C. | 3:05 | 30.28 | 22.06 | 1.00 | 32.22 | 0.604 | 76.47 | 76.46 |
| E. F. D. B. 5/15/14 | 75.02 | Preliminary | A. M. 10:50 | | | | | | | |
| | | 2d Hr. P. C. | 11:50 | 29.60 | 22.91 | 0.94 | 29.06 | 0.534 | 78.74 | 77.76 |
| | | 3d Hr. P. C. | P. M. 12:50 | 31.35 | 22.12 | 1.03 | 30.02 | 0.534 | 77.26 | 80.09 |
| | | 4th Hr. P. C. | 1:50 | 31.07 | 24.04 | 0.94 | 30.73 | 0.534 | 82.67 | 80.28 |
| | | 5th Hr. P. C. | 2:50 | 29.95 | 22.21 | 0.98 | 30.87 | 0.534 | 76.96 | 79.99 |
| | | 6th Hr. P. C. | 3:50 | 28.46 | 22.57 | 0.92 | 30.46 | 0.534 | 77.11 | 75.02 |

—Data in Hourly Periods

| Direct Calorimetry Cal. | Rectal Temperature, C. | Av. Pulse | Work-Adder, Cm. | Non-Protein R. Q. | Per Cent. Calories from | | | Calories Per Hour | | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Prot. | Fat | Carb. | Per Kg. | Per Sq. M. | |
| | 37.26 | | | | | | | | | |
| 78.95 | 37.30 | .. | .... | 0.87 | 18 | 37 | 45 | 0.92 | 32.07 | Basal. |
| 82.80 | 37.25 | 62 | .... | 0.74 | 15 | 77 | 8 | 1.08 | 37.61 | Basal. |
| 84.21 | 37.28 | 88 | .... | 0.75 | 11 | 77 | 12 | 1.20 | 41.72 | At 11:53 a. m., 115 gm. commercial glucose. |
| 86.54 | 37.30 | .. | .... | .... | 12 | .. | .. | 1.11* | 38.46* | |
| 92.88 | 37.17 | .. | .... | 0.96 | 13 | 11 | 76 | 1.03 | 35.84 | |
| | 36.88 | | | | | | | | | |
| 78.09 | 36.90 | .. | .... | 0.78 | 18 | 62 | 20 | 1.13 | 38.63 | Basal. |
| 72.10 | 36.91 | 59 | .... | 0.88 | 20 | 33 | 47 | 0.98 | 33.19 | Basal. |
| 87.12 | 36.84 | 57 | .... | 0.94 | 21 | 16 | 63 | 1.10 | 37.13 | At 11:38 a. m., 115 gm. commercial glucose. |
| 83.46 | 36.87 | 64 | .... | 0.91 | 19 | 25 | 56 | 1.18 | 39.97 | |
| 85.60 | 36.98 | .. | .... | 0.91 | 19 | 26 | 55 | 1.15 | 39.04 | |
| 84.64 | 36.99 | 60 | .... | 0.93 | 20 | 19 | 61 | 1.11 | 37.89 | |
| | 36.96 | | | | | | | | | |
| 62.89 | 36.81 | 57 | 22 | 0.83 | 19 | 47 | 34 | 0.99 | 33.95 | Basal. |
| 77.00 | 36.80 | 55 | 13 | 0.85 | 19 | 41 | 40 | 0.97 | 33.45 | Basal. |
| 74.42 | 36.98 | .. | 10 | 0.87 | 19 | 36 | 45 | 0.95 | 32.46 | Basal. |
| | 36.84 | | | | | | | | | At 8:55 a. m., 230 gm. commercial glucose. |
| 72.90 | 36.75 | 66 | 15 | 1.03 | 19 | 0 | 81 | 1.05 | 36.08 | |
| 82.51 | 26.84 | 63 | 17 | 1.02 | 19 | 0 | 81 | 1.09 | 37.38 | |
| 84.53 | 36.95 | 60 | 14 | | | | | | | |
| 82.50 | 37.01 | 58 | 16 | 0.99 | 19 | 2 | 79 | 1.07 | 36.64 | |
| 79.32 | 37.00 | 60 | 24 | | | | | | | |
| | 36.91 | | | | | | | | | |
| 110.72 | 36.88 | 54 | 30— | 0.82 | 19 | 51 | 30 | 0.96 | 32.86 | Basal. |
| 116.62 | 36.99 | 56 | 37— | 0.78 | 18 | 62 | 20 | 1.03 | 35.29 | Basal. |
| | 36.84 | | | | | | | | | At 9:54 a. m., protein meal (10.5 gm. N). |
| 84.05 | 36.91 | 57 | 24— | 0.83 | 28 | 42 | 30 | 1.07 | 36.79 | |
| 77.92 | 36.89 | 57 | 28— | 0.83 | 25 | 43 | 32 | 1.16 | 39.72 | |
| 86.71 | 36.93 | 58 | 30— | 0.81 | 29 | 46 | 25 | 1.12 | 38.21 | |
| 81.62 | 36.94 | 57 | 25— | 0.81 | 18 | 53 | 29 | 1.15 | 39.36 | |
| 88.88 | 37.04 | 56 | 33— | 0.83 | 19 | 46 | 35 | 1.06 | 36.39 | |
| | 36.66 | | | | | | | | | |
| 75.09 | 36.67 | 61 | 14.1 | 0.99 | 20 | 3 | 77 | 1.08 | 36.86 | At 10:05-10:07 a. m., 200 gm. dextrose. |
| 83.22 | 36.78 | 61 | 23.5 | 0.96 | 19 | 11 | 70 | 1.11 | 38.02 | |
| 73.61 | 36.78 | 61 | 18.8 | 0.99 | 21 | 2 | 77 | 1.03 | 35.39 | |
| 76.05 | 36.79 | 62 | 26.0 | 1.06 | 21 | .. | 79 | 1.02 | 35.00 | |
| | 36.69 | | | | | | | | | |
| 78.53 | 36.72 | 55 | 19.6 | 0.97 | 18 | 8 | 74 | 1.05 | 35.95 | At 9:50-9:53 a. m., 200 gm. dextrose. |
| 78.50 | 36.73 | 58 | 22.5 | 1.00 | 18 | .. | 82 | 1.06 | 35.28 | |
| 79.13 | 36.73 | 59 | 23.1 | 0.97 | 17 | 8 | 75 | 1.10 | 37.75 | (Carbohydrate breakfast at 6:15 a. m.). |
| 81.32 | 36.76 | 59 | 21.8 | 1.03 | 18 | .. | 82 | 1.06 | 35.14 | |
| 72.36 | 36.74 | 57 | 34.0 | 0.95 | 18 | 15 | 67 | 1.03 | 35.21 | |

* Estimated from $CO_2$.

TABLE 2.—

| Subject Date | Weight Kg. | Period | End of Period | $CO_2$, Gm. | $O_2$ Gm. | R. Q. | $H_2O$, Gm. | Urine N Per Hour, Gm. | Indirect Calorimetry, Cal. | Heat Eliminated, Cal. |
|---|---|---|---|---|---|---|---|---|---|---|
| E. F. D. B. 5/18/14 | 73.70 | Preliminary | 10:50 | | | | | | | |
| | | 1st Hr. ..... | 11:50 P. M. | 23.92 | 21.68 | 0.83 | 28.03 | 0.530 | 70.29 | 67.48 |
| | | 2d Hr. ..... | 12:50 A. M. | 23.85 | 21.88 | 0.79 | 28.08 | 0.530 | 72.38 | 69.37 |
| F. C. G. ... 3/17/13 | 56.5 | Preliminary | 9:02 | | | | | | | |
| | | 1st Hr. ..... | 10:02 | 22.80 | ..... | .... | 17.77 | 0.491 | ..... | 54.43 |
| | | 2d Hr. ..... | 11:02 P. M. | 22.92 | ..... | .... | 19.69 | 0.491 | ..... | 59.16 |
| | | 3d Hr. ..... | 12:02 | 22.59 | ..... | .. . | 20.90 | 0.491 | ..... | 60.70 |
| F. C. G. ... 3/17/13 | 56.5 | Preliminary | 1:00 | | | | | | | |
| | | 2d Hr. P. C. | 2:00 | 14.86 | 41.52 | 0.85 | 23.05 | 0.491 | 139.35 | 60.85 |
| | | 3d Hr. P. C. | 3:00 | 23.53 | 21.08 | | 30.51 | 0.491 | | 68.89 |
| | | 4th Hr. P. C. | 4:00 A. M. | 22.73 | 25.27 | 0.78 | 26.08 | 0.491 | 69.59 | 62.52 |
| F. C. G. ... 4/22/13 | 54.82 | Preliminary | 9:45 | | | | | | | |
| | | 1st Hr. ..... | 10:45 | 21.92 | ..... | .... | 25.40 | ..... | ..... | 58.96 |
| | | 2d Hr. ..... | 11:45 P. M. | 22.05 | ..... | .... | 26.85 | ..... | ..... | 61.94 |
| | | 3d Hr. ..... | 12:45 | 21.08 | ..... | .... | 26.26 | ..... | ..... | 62.60 |
| | | 4th Hr. ..... | 1:45 | 21.86 | ..... | .... | 28.59 | ..... | ..... | 63.33 |
| | | 5th Hr. ..... | 2:45 A. M. | 22.03 | ..... | .... | 30.09 | ..... | ..... | 68.43 |
| R. H. H. ... 3/19/13 | 62.00 | Preliminary | 9:42 | | | | | | | |
| | | 1st Hr. ..... | 10:42 | 26.15 | 21.59 | 0.88 | 27.90 | ..... | 73.54 | 66.50 |
| | | 2d Hr. ..... | 11:42 A. M. | 27.42 | 20.98 | 0.95 | 28.93 | ..... | 72.78 | 69.27 |
| Louis M. ... 3/26/13 | 51.70 | Preliminary | 10:10 | | | | | | | |
| | | 1st Hr. ..... | 11:10 P. M. | 20.53 | 18.73 | 0.80 | 28.92 | 0.522 | 61.91 | 64.64 |
| | | 2d Hr. ..... | 12:10 | 19.95 | 17.40 | 0.83 | 26.95 | 0.522 | 57.99 | 64.44 |
| | | 3d Hr. ..... | 1:10 | 22.44 | 20.07 | 0.81 | 28.10 | 0.522 | 66.57 | 71.00 |
| | | 4th Hr. ..... | 2:10 | 18.34 | 18.05 | 0.74 | 25.73 | 0.522 | 58.71 | 66.51 |
| | | 5th Hr. ..... | 3:10 | 22.13 | 20.71 | 0.78 | 27.36 | 0.522 | 68.20 | 68.38 |
| | | 6th Hr. ..... | 4:10 A. M. | 19.36 | 19.23 | 0.73 | 25.85 | 0.522 | 62.51 | 67.86 |
| Louis M. ... 3/28/13 | 53.49 | Preliminary | 11:14 P. M. | | | | | | | |
| | | 3d Hr. P. C. | 12:14 | 23.43 | 22.62 | 0.75 | 24.08 | 0.703 | 73.76 | 64.89 |
| | | 4th Hr. P. C. | 1:14 | 24.27 | 22.67 | 0.78 | 29.15 | 0.695 | 74.44 | 75.48 |
| | | 5th Hr. P. C. | 2:14 | 26.84 | 25.11 | 0.78 | 34.80 | 0.970 | 82.02 | 79.07 |
| | | 6th Hr. P. C. | 3:14 | 26.44 | 25.11 | 0.77 | 34.38 | 1.014 | 81.70 | 77.18 |
| | | 7th Hr. P. C. | 4:14 | 24.85 | 23.21 | 0.78 | 35.42 | 1.138 | 75.38 | 83.35 |
| | | 8th Hr. P. C. | 5:14 A. M. | 26.25 | 24.79 | 0.77 | 34.71 | 1.112 | 80.53 | 81.28 |
| John L. .... 3/26/14 | 70.94 | Preliminary | 11:20 P. M. | | | | | | | |
| | | 1st Hr. ..... | 12:20 | 21.12 | 19.51 | 0.79 | 25.77 | 0.363 | 64.65 | 66.00 |
| | | 2d Hr. ..... | 1:20 | 21.37 | 19.62 | 0.79 | 24.56 | 0.363 | 65.10 | 68.26 |
| | | 3d Hr. ..... | 2:20 A. M. | 21.07 | 19.97 | 0.77 | 24.01 | 0.363 | 65.85 | 66.72 |
| L. C. M. .. 5/4/14 | 59.50 | Preliminary | 11:02 P. M. | | | | | | | |
| | | 1st Hr. ..... | 12:02 | 22.39 | 20.71 | 0.79 | 28.32 | 0.534 | 68.34 | 71.73 |
| | | 2d Hr. ..... | 1:02 A. M. | 22.14 | 18.98 | 0.85 | 27.28 | 0.534 | 63.57 | 70.36 |
| L. C. M. .. 5/6/14 | 60.98 | Preliminary | 10:52 | | | | | | | |
| | | 2d Hr. P. C. | 11:52 P. M. | 29.94 | 23.73 | 0.92 | 33.43 | 0.578 | 81.05 | 73.19 |
| | | 3d Hr. P. C. | 12:52 | 30.30 | 22.03 | 1.00 | 32.38 | 0.578 | 76.45 | 74.95 |
| | | 4th Hr. P. C. | 1:52 | 30.65 | 21.90 | 1.02 | 32.94 | 0.578 | 76.21 | 77.37 |

—(Continued)

| Direct Calorimetry Cal. | Rectal Temperature, C. | Av. Pulse | Work-Adder, Cm. | Non-Protein R. Q. | Per Cent. Calories from | | | Calories Per Hour | | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Prot. | Fat | Carb. | Per Kg. | Per Sq. M. | |
| | 36.76 | | | | | | | | | |
| 67.14 | 36.76 | 57 | 9.8 | 0.83 | 20 | 46 | 34 | 0.95 | 32.48 | Basal. |
| 70.23 | 36.78 | 57 | 18.2 | 0.79 | 19 | 58 | 23 | 0.98 | 33.45 | |
| | 37.03 | | | | | | | | | |
| 58.83 | 37.15 | .. | .... | .... | .. | .. | .. | 1.04 | 30.75 | Basal. Profound sleep during second and third periods. $O_2$ leak. |
| 55.75 | 37.11 | .. | .. . | .... | .. | .. | .. | 0.99 | 32.45 | |
| 56.99 | 37.06 | .. | .... | .... | .. | .. | . | 1.01 | 31.43 | |
| | 37.02 | | | | | | | | | |
| 66.85 | 37.17 | .. | .... | 0.86 | 19 | 39 | 42 | 1.18 | 36.87 | At 12 m., plate of oatmeal. $O_2$ leak. |
| 60.53 | 37.00 | .. | .... | | | | | 1.07 | 33.39 | |
| 60.82 | 36.95 | .. | .... | 0.78 | 19 | 61 | 20 | 1.08 | 33.59 | |
| | 37.04 | | | | | | | | | |
| 57.28 | 37.03 | 74 | .... | .. . | .. | .. | .. | 1.04 | 32.22 | Basal. $O_2$ leak. |
| 62.68 | 37.07 | 68 | .... | .... | .. | . | .. | 1.14 | 35.25 | |
| 60.60 | 37.04 | 64 | . .. | .... | .. | .. | .. | 1.10 | 34.08 | |
| 58.15 | 36.94 | 66 | .... | .... | .. | .. | .. | 1.06 | 32.71 | |
| 64.88 | 36.87 | 70 | .... | .... | .. | .. | .. | 1.18 | 36.49 | |
| | 36.76 | | | | | | | | | |
| 69.22 | 36.82 | .. | ... | . . | .. | .. | .. | 1.19 | 38.12 | Basal. Urine not obtained. |
| 70.31 | 36.85 | . | .... | .... | .. | .. | .. | 1.19 | 37.73 | |
| | 37.18 | | | | | | | | | |
| 58.39 | 37.07 | .. | .... | 0.80 | 22 | 56 | 24 | 1.20 | 36.23 | Basal. |
| 61.88 | 37.04 | .. | .... | 0.84 | 24 | 40 | 36 | 1.12 | 33.92 | |
| 75.26 | 37.15 | .. | .... | 0.82 | 21 | 49 | 30 | 1.29 | 38.95 | |
| 59.27 | 37.00 | .. | .... | 0.72 | 24 | 73 | 3 | 1.14 | 34.35 | |
| 70.95 | 37.08 | .. | .... | 0.77 | 20 | 63 | 17 | 1.32 | 39.91 | |
| 62.47 | 36.98 | .. | .... | 0.71 | 22 | 77 | 1 | 1.21 | 36.58 | |
| | 37.10 | | | | | | | | | |
| 74.89 | 37.28 | .. | .. . | 0.74 | 25 | 68 | 7 | 1.39 | 42.20 | 8:25-9:25 a. m., 725 gm. chopped beef = 23.93 gm. N + 100 gm. fat. |
| 81.49 | 37.43 | .. | .... | 0.77 | 25 | 59 | 16 | 1.40 | 42.59 | |
| 74.67 | 37.36 | .. | .... | 0.76 | 31 | 55 | 14 | 1.54 | 46.92 | |
| 78.43 | 37.41 | .. | .... | 0.75 | 33 | 58 | 9 | 1.54 | 46.74 | |
| 80.09 | 37.38 | .. | .... | 0.76 | 40 | 49 | 11 | 1.42 | 43.12 | |
| 81.96 | 37.39 | .. | . .. | 0.75 | 37 | 54 | 9 | 1.51 | 46.07 | |
| | 37.11 | | | | | | | | | |
| 52.70 | 36.89 | 61 | 13.0+ | 0.78 | 15 | 62 | 23 | 0.91 | 30.64 | Basal. |
| 68.56 | 36.94 | 55 | 13.0+ | 0.79 | 15 | 61 | 24 | 0.92 | 30.85 | |
| 62.04 | 36.88 | 57 | 38.7 | 0.76 | 15 | 69 | 16 | 0.92 | 31.21 | |
| | 36.94 | | | | | | | | | |
| 66.95 | 36.85 | 74 | 22.0+ | 0.78 | 21 | 59 | 20 | 1.15 | 36.41 | Basal. |
| 73.48 | 36.92 | 70 | 18.2 | 0.86 | 22 | 37 | 41 | 1.07 | 33.87 | |
| | 36.84 | | | | | | | | | |
| 65.74 | 36.70 | 85 | 19.1 | 0.95 | 19 | 15 | 66 | 1.33 | 42.48 | 9:50-9:53 a. m., dextrose, 200 gm. |
| 73.60 | 36.68 | 82 | 30.1 | 1.06 | 20 | .. | 80 | 1.25 | 40.07 | |
| 82.59 | 36.79 | 79 | 38.2 | 1.08 | 20 | .. | 80 | 1.25 | 39.94 | |

The results are expressed in terms of grams and calories per hour, since this is the length of period used in the Cornell and Sage calorimeters and is the nearest unit of the length of the actual experimental period used in most of the modern machines.

## DISCUSSION OF RESULTS

As explained in Paper 1 of this series, the determination of the heat production by the methods of direct and indirect calorimetry have been found to give identical results in the work of Rubner, Atwater and Benedict, Lusk and his coworkers. Rubner demonstrated this on the dog in long periods, Atwater and Benedict on man at rest and at work, Lusk on dogs in hourly periods and Howland, in Lusk's laboratory, on babies both normal and atrophic. To this list may be added the work of Armsby[19] on cattle in twenty-four-hour experiments and the work of Carpenter and Murlin[20] who studied the metabolism of women before and after confinement, in Benedict's laboratory. A comparison of the figures for direct and indirect calorimetry obtained in Benedict's calorimeter shows excellent agreement in the two- and three-hour periods. Out of a total of twenty-eight periods, the two methods were within 5 per cent. of each other in seventeen, while only six showed a disagreement over 10 per cent.

Table 3 gives in parallel columns the calories in each of our experiments as measured by the methods of direct and indirect calorimetry. The totals of all the experiments show that the two methods come within 0.17 per cent. of each other. Even when we consider periods as short as one hour, the agreement may be striking. On the normal control, E. F. D. B., there were a total of 26 one-hour periods. In 17 of these the methods of direct and indirect calorimetry agreed within 5 per cent., in 6 periods within 6 to 9 per cent., while three isolated periods showed a disagreement of 11, 12 and 16 per cent., respectively. Work with the Sage calorimeter on normal controls and on patients with a large variety of diseases has shown that in a total measurement of 27,632 calories the direct calorimetry gives a figure only 1.62 per cent. lower than the indirect. There is, therefore, no reason to believe that in long periods, or in the average of a number of short periods, there is any essential difference between the two methods. As will be shown later, there is good reason to believe that indirect calorimetry gives the more accurate results in short periods.

There are two methods of calculating the indirect calorimetry, both of which involve factors that change with the respiratory quotient.

19. Armsby: Food as Body Fuel, Pennsylvania State College Agricultural Experiment Station, Bull. 126.

20. Carpenter and Murlin: The Energy Metabolism of Mother and Child Just Before and Just After Birth, THE ARCHIVES INT. MED., 1911, vii, 184.

TABLE 3.—Summary of Results. Averages of Periods

| Subject | Date | Weight at Start, Kg. | Square Meters Body Surface (Meeh) | Calories per Sq. M. per Hour | Variation from Average Normal Basal 34.7 | Per Cent. Rise above Subject's Own Basal Metabolism | Average R. Q. | Total Calories Measured in Each Experiment | | Method of Direct Calorimetry Surface Temperature | Character of Experiment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Method of Indirect Calorimetry | Method of Direct Calorimetry Rectal Temp. | | |
| G. L. ..... | 3/11/13 | 78.42 | 2.256 | 34.84 | + 0 | .. | 0.80 | 157.40 | 161.75 | ..... | Two basal hours. |
| | 3/11/13 | 78.42 | 2.256 | 38.67 | .... | 11 | .... | 261.54 | 273.63 | ..... | First three hours after 115 Comm. glucose = 100 C. P. dextrose |
| E. F. D. B. | 3/13/13 | 73.6 | 2.162 | 35.91 | + 3 | .. | 0.82 | 155.27 | 149.79 | ..... | Two basal hours. |
| | 3/13/13 | 73.6 | 2.162 | 38.51 | .... | 7 | 0.90 | 333.02 | 341.22 | ..... | First three hours after 115 Comm. glucose = 100 C. P. dextrose |
| | 5/17/13 | 75.51 | 2.200 | 33.29 | − 4 | .. | 0.84 | 219.70 | 214.31 | ..... | Three basal hours. |
| | 5/22/13 | 76.10 | 2.211 | 36.82 | .... | 11 | 0.97 | 407.11 | 401.96 | ..... | 1½ to 5½ hours after 220 Comm. glucose = 200 C. P. dextrose. |
| | 3/30/13 | 74.34 | 2.177 | 34.08 | − 2 | .. | 0.80 | 222.50 | 227.34 | 232.23 | Three basal hours. |
| | 4/ 1/13 | 74.92 | 2.188 | 38.09 | .... | 12 | 0.82 | 416.75 | 419.18 | 413.58 | 1½ to 6½ hours after protein meal (10.5 gm. N). |
| | 5/ 8/13 | 74.75 | 2.185 | 36.32 | .... | 10 | 0.96 | 317.41 | 307.97 | 317.60 | 1 to 5 hours after 200 C. P. dextrose. |
| | 5/15/13 | 75.02 | 2.190 | 35.87 | .... | 9 | 0.96 | 392.74 | 389.94 | 395.82 | 1 to 6 hours after 200 C. P. dextrose taken 3½ hours after breakfast |
| | 5/18/13 | 73.70 | 2.164 | 32.97 | − 5 | .. | 0.81 | 142.67 | 137.37 | 138.33 | Two basal hours. |
| F. C. G. .. | 3/17/13 | 56.5 | 1.813 | 31.54 | − 9 | .. | .... | * | ..... | ..... | Three basal hours.. |
| | 3/17/13 | 56.5 | 1.813 | 34.60 | .... | 10 | .... | * | ..... | ..... | 1 to 4 hours after breakfast of protein 13.1, fat 10.2, carbohydrate 35.5 |
| | 4/22/13 | 54.82 | 1.778 | 34.15 | − 2 | .... | .... | 146.32 | 139.53 | ..... | Five hours basal. |
| R. H. H. .. | 3/19/13 | 62.00 | 1.929 | 37.93 | + 9 | .. | 0.92 | 146.32 | 139.53 | ..... | Two hours basal. |
| Louis M. .. | 3/26/13 | 51.70 | 1.709 | 36.66 | + 6 | .. | 0.78 | 375.89 | 388.22 | ..... | Six hours basal. |
| | 3/28/13 | 53.49 | 1.748 | 44.61 | .... | 22 | 0.77 | 467.83 | 471.53 | ..... | 2 to 8 hours after 725 gm. beef = 23.93 N and 100 fat |
| John L. .. | 3/26/14 | 70.94 | 2.110 | 30.90 | −11 | .. | 0.78 | 195.60 | 183.30 | 188.50 | Three hours basal. |
| L. C. M. .. | 5/ 4/14 | 59.50 | 1.887 | 35.14 | + 1 | .. | 0.82 | 131.91 | 140.43 | 141.73 | Two hours basal.. |
| | 5/ 6/14 | 60.98 | 1.908 | 40.83 | .... | 16 | 0.98 | 233.71 | 221.93 | 225.28 | 1 to 4 hours after 200 gm. C. P. dextrose. |
| Total ..... | | | | | | | | 4577.37 | 4569.40 | | ..... |

* Oxygen figures discarded on account of leaks.

The first is the standard method of Zuntz and his associates, based on the liters of oxygen consumed, which are multiplied by a factor that increases about 8 per cent. as the quotient rises from 0.72 to 0.97. The second method is based on the liters of $CO_2$ produced, the figure for which is multiplied by a factor which decreases 24 per cent. as the

TABLE 4.—HEAT PRODUCTION OF NORMAL MEN, AGES 20 TO 50. COMPARISON OF CALORIES PER KILOGRAM AND PER SQUARE METER

| Subject | Weight, Kg. | Calories per Kilogram per Hour | Calories per Sq. Meter per Hour | Percentage Variation from Average | | Calories per Sq. Meter per Hour According to New Surface Area Formula | Per Cent. Variation from Average |
|---|---|---|---|---|---|---|---|
| | | | | Calories per Kg. | Calories per Sq. Meter | | |
| F. G. B.* | 83.0 | 1.01 | 35.8 | − 4 | + 5 | .... | ... |
| G. L. | 78.4 | 1.00 | 34.8 | − 5 | + 2 | 40.7 | +2 |
| F. A. R.* | 74.3 | 0.95 | 32.4 | − 9 | − 5 | .... | ... |
| E. F. D. B. | 74.3 | 1.00 | 34.1 | − 5 | 0 | 39.8 | −0 |
| John L. | 70.9 | 0.92 | 30.9 | −12 | −10 | .... | ... |
| J. J. C.* | 67.6 | 0.96 | 31.7 | − 8 | − 7 | .... | ... |
| J. R.* | 66.0 | 1.00 | 32.8 | − 5 | − 4 | .... | ... |
| R. H. H. | 62.0 | 1.18 | 37.9 | +14 | +11 | 40.9 | +3 |
| L. C. M. | 59.5 | 1.11 | 35.1 | + 6 | + 3 | 40.5 | +2 |
| F. C. G. | 54.8 | 1.10 | 34.2 | + 5 | 0 | 37.7 | −5 |
| Louis M. | 51.7 | 1.21 | 36.7 | +16 | + 7 | .... | ... |
| T. M. C.* | 49.0 | 1.13 | 33.8 | + 8 | − 1 | .... | ... |
| Average | .... | 1.05 | 34.2 | ± 8.1 | ± 4.6 | 39.9 | ±2.4 |
| 79 normal men in groups† | | | | | | | |
| 8 weights | 75-85 | 1.01 | 35.2 | − 7 | + 2 | .... | ... |
| 20 weights | 65-75 | 1.02 | 34.1 | − 6 | − 2 | .... | ... |
| 41 weights | 55-65 | 1.09 | 34.7 | + 1 | 0 | .... | ... |
| 10 weights | 45-55 | 1.18 | 35.5 | + 9 | + 2 | .... | ... |
| Average | ..... | 1.08 | 34.7 | ± 5.8 | ± 1.5 | .... | ... |

* Determinations made by Benedict and Joslin.[20]
† Taken largely from work of Benedict, Emmes, Roth and Smith,[10]

quotient rises from 0.72 to 0.97. Tables for this latter calculation are given by Benedict and Talbot,[21] who prefer this method in using an apparatus in which they consider that for short periods the determination of the carbon dioxid is more exact than the determination of

21. Benedict and Talbot: Studies in the Respiratory Exchange of Infants, Am. Jour. Dis. Child., 1914, viii, 1; The Gaseous Metabolism of Infants, Carnegie Institution of Washington, Pub. 201.

oxygen. It is true that in the closed circuit type of apparatus the measurement of the oxygen is subject to many corrections for changes in the barometer, temperature, moisture, etc., and that it is liable to a plus error in the case of leaks. This error affects the quotient and produces such a change in the $CO_2$ factor that one usually obtains better results by basing the calculations on the oxygen. This is brought out clearly in Table 5, which gives a comparison of the methods of calculating the heat production from the oxygen and from the $CO_2$, showing the errors in the results arising from various assumed errors in the measurements. It will be noted that in the great majority of the cases

TABLE 5.—Comparison of Methods of Calculation with Assumed Errors in Measurement of $CO_2$ and $O_2$

| $CO_2$ | | $O_2$ | | R.Q. | Calorific Value 1 Liter of $CO_2$ | | Calorific Value 1 Liter of $O_2$ | | Indirect Calorimetry Based on $CO_2$ | | Indirect Calorimetry Based on $O_2$ | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Liters | Assumed Error % | Liters | Assumed Error % | | Cal. | Per Cent. Change | Cal. | Per Cent. Change | Cal. | Per Cent. Error | Cal. | Per Cent. Error |
| 12.94 | 0 | 15.64 | 0 | 0.83 | 5.829 | ..... | 4.807 | ..... | 75.40 | ..... | 75.17 | ..... |
| 12.94 | 0 | 17.20 | +10 | 0.75 | 6.319 | +8.4 | 4.708 | −2.1 | 81.74 | +8.4 | 80.98 | +7.7 |
| 14.22 | +10 | 15.64 | 0 | 0.91 | 5.424 | −7.0 | 4.904 | +2.0 | 77.18 | +2.4 | 76.70 | +2.0 |
| 12.94 | 0 | 16.42 | +5 | 0.79 | 6.062 | +4.0 | 4.756 | −1.1 | 78.44 | +4.0 | 78.13 | +3.9 |
| 13.59 | +5 | 15.64 | 0 | 0.87 | 5.617 | −3.6 | 4.855 | +1.0 | 76.33 | +1.2 | 75.93 | +1.0 |
| 12.29 | −5 | 16.42 | +5 | 0.75 | 6.219 | +8.4 | 4.708 | −2.1 | 77.66 | +3.0 | 77.31 | +2.8 |
| 13.59 | +5 | 14.86 | −5 | 0.91 | 5.424 | −7.0 | 4.904 | +2.0 | 73.71 | −2.2 | 72.87 | −3.1 |
| 12.94 | 0 | 14.86 | −5 | 0.87 | 5.617 | −2.7 | 4.855 | +1.0 | 72.68 | −3.6 | 72.15 | −4.0 |

cited the error from the use of the oxygen factor is smaller than that from the $CO_2$. Even with a plus error of 5 to 10 per cent. in the oxygen and no error in the $CO_2$, the results obtained by using the oxygen are the better, since the minus change in this factor compensates for part of the error. In the two instances shown, in which the results obtained by the use of the $CO_2$ factor are closer to the theory than those obtained by the use of the oxygen factor, it will be noted that there is a minus error in the oxygen. This is the least frequent of all the errors.

Many investigators in seeking for an index of the heat production express the results in grams or cubic centimeters of $CO_2$, and compare the elimination of this gas in different individuals, apparently with the impression that they are comparing the actual total metabolism. As we have seen above, a man eliminating, say, 3.13 c.c. $CO_2$ per kg. per min-

ute might have a heat production 24 per cent. higher than another man eliminating the same amount of $CO_2$ whose respiratory quotient was at the other end of the scale. If one uses the oxygen consumption the possible error from this source is diminished to 8 per cent. Since it is such an easy calculation to determine the actual calories by using the oxygen figure and the respiratory quotient, it seems inexcusable to leave the results at a stage which might give false impressions. It is only in special investigations on the ventilation of the lungs, etc., that the amounts of the gases themselves are of any direct interest. In most experiments it is the actual calories that need to be determined.

Experience has shown that with careful technic the indirect calorimetry in hourly periods remains fairly uniform in fasting experiments and shows regular curves in experiments after food. The direct calorimetry in hourly periods is a matter of greater technical difficulty on account of the fact that the human body is poorly constructed for accurate thermal measurements. As was shown in Paper 1, a rise or fall of 1 degree centigrade in the average temperature of the body means a storage or loss of about 58 calories if the man weighs 70 kilograms. This is based on the assumption that the specific heat of the body is 0.83, a figure which has been accepted for many decades, although without satisfactory experimental support. Rubner[22] has found that the specific heat of lean flesh is 0.828, of fatty tissue 0.53 and of pure fat 0.45. Rosenthal[23] at an earlier date had made the following determinations: compact bone 0.30, spongy bone 0.710, defibrinated blood 0.927, dried muscle 0.330. Using these figures and the figures for the average composition of the body as given by Vierort[24] one obtains a specific heat of approximately 0.77. A body rich in fat would, of course, approach the figure 0.45 and one rich in water would approach 1.00. Theoretically, one should change the specific heat each time a subject drinks water or voids. This latter would be a matter of small importance, but in the case of a very obese person one-half of whose weight consisted of fat, the true specific heat would not be far from 0.64.

In normal subjects the temperature changes in hourly periods are small and according to the work of Benedict and Slack,[25] the temper-

22. Rubner: Kalorimetrie, Tigerstedt's Handbuch der physiologische Methoden, i, 170.

23. Rosenthal: Ueber die specifische Wärme thierische Gewebe, Arch. f. Physiol., 1878, p. 215.

24. Vierort: Daten und Tabellen. Jena, 1893, p. 249.

25. Benedict and Slack: A Comparative Study of the Temperature Fluctuation in Different Parts of the Human Body. Carnegie Institution of Washington, 1911, Pub. 155.

ature curves in different parts of the body are nearly parallel. Lusk[26] and his coworkers did not find this to be the case in the dog after the ingestion of large amounts of food since this caused a greater rise in surface than in rectal temperature. When one considers the mechanism of the regulation of body temperature in fever it becomes evident that the rise in surface temperature follows that of the internal temperature. Every clinician has felt in some patients, particularly those seriously ill, the extremities growing colder and colder while the internal temperature is rising and, conversely, has felt the surface grow warmer while the temperature is falling, demonstrating the fact that the two are not always parallel.

It was on account of these considerations that the surface thermometers described in Paper 2 were used after May, 1913, the two units of the surface thermometer being strapped over the right and left pectoralis major as near as possible to the heart and dome of the liver. They were covered with a thick layer of cotton in an effort to obtain the temperature of the subcutaneous tissue rather than that of the naked skin. After March 12, 1914, a second surface thermometer was added and its two units placed in various parts of the anterior surface of the thorax and abdomen and also in the axillae. The results have been confusing and difficult to interpret, but they have indicated clearly that the different parts of the body do not show parallel temperature curves. A fruitless search has been made for some part of the body which will give a true index of the mean temperature change. In the majority of all the experiments the rectal temperature was the more satisfactory, but in typhoid fever the surface gave better results. The method of investigation was as follows:

In a total of eighty-five experiments satisfactory rectal and surface temperature measurements were made. Twenty-eight of these experiments were on typhoid fever patients. For the reasons above stated the heat production as determined by the method of indirect calorimetry was considered to be the true heat production, and the results of the direct calorimetry as calculated by three different methods were compared with this as shown in the table below. In all three methods the figure for the heat eliminated from the body was, of course, the same. To obtain the heat produced, the heat stored in or lost from the body, as determined by each of the two measurements, and by a mean of the two, has been added to or subtracted from the heat eliminated.

It will be seen from Table 6 that in the total of 85 experiments the rectal temperature gave the best results, approximating the theoretical more closely than either of its competitors in 36 cases, coming within 5

26. Williams, Riche and Lusk: Metabolism of the Dog Following the Ingestion of Meat in Large Quantity, Jour. Biol. Chem., 1912, xii, 349.

per cent. in 62 cases and involving a total error of only 0.90 per cent. While the surface temperature gave the best results in 24 cases, it showed an error of over 15 per cent. in 5 cases and did not prove as reliable as the mean of surface and rectal. In typhoid fever the honors were more evently divided and all three methods gave surprisingly good results in spite of the large changes in body temperature sometimes encountered. The surface temperature alone gave the best results in 13 of the 28 experiments and also the lowest total error.

TABLE 6.—Comparison of Surface and Rectal Temperatures as an Index of Average Body Temperature; Percentage Differences between Indirect Calorimetry and Direct Calorimetry Calculated According to Three Methods

| Percentage Difference in Individual Experiments | Number of Experiments Falling in Each Group | | | | | |
|---|---|---|---|---|---|---|
| | Twenty-Eight Typhoid Experiments | | | Eighty-Five Experiments in Various Diseases, Including the Twenty-Eight Typhoid Observations | | |
| | Rectal Temperature Alone | Surface Temperature Alone | One-half Rectal, One-half Surface | Rectal Temperature Alone | Surface Temperature Alone | One-half Rectal, One-half Surface |
| 0 to 5 | 18 | 18 | 18 | 62 | 41 | 53 |
| 5 to 10 | 9 | 9 | 10 | 19 | 28 | 27 |
| 10 to 15 | 1 | 1 | 0 | 4 | 11 | 4 |
| 15+ | 0 | 0 | 0 | 0 | 5 | 1 |
| Total difference | −1.32 | −1.17 | −1.24 | −0.90 | −1.46 | −1.18 |
| Number giving results nearest to indirect | 8 | 13 | 7 | 46 | 24 | 15 |

As a result of the above analysis the rectal temperature has been adopted as the standard indicator of the average body change in hourly periods, but with a full realization of its limitations. In many experiments, particularly in those with rapidly changing temperature, better results would be obtained by using the surface temperature, but surface thermometers are more easily displaced than rectal and are not so reliable in the long run. Theoretically, one would obtain the best results by the use of many thermometers placed in the rectum, axillae, groin, on the surface of the body in many areas, giving each measurement an estimated weight, and then calculating the mean temperature change. Our attempt to do this in a small way by giving the rectal and surface equal weights did not lead to better results. For many reasons it seems advisable to attach as little apparatus as possible to the subject, and it is

doubtful if the use of many thermometers at one time will ever become a standard method.

There may be several reasons why these results are not in accord with the conclusion of Benedict and Slack. Working with normal subjects who showed comparatively small fluctuations in body temperature, they made many measurements at different depths in the rectum and vagina and found that while there was a sharp fall in temperature between a point 7 cm. within the rectum and a point just within the anus, nevertheless the temperature of points at different depths remained parallel, though at a different level. Temperatures taken in the well-closed axilla and groin were also parallel with the rectal. The mouth was found to be an unsatisfactory place to obtain the mean body temperature. Considerable difficulty was experienced in obtaining satisfactory measurements of the surface of the body and of the hands, and the writers speak of the difficulty of devising a thermometer that will be shielded so that it may assume the body temperature and yet not interfere with the natural liberation of heat.

As we have mentioned above, our surface thermometers were covered with a thick layer of cotton wool and represented a subcutaneous rather than a surface measurement, and therefore not comparable to the axillary, groin and shallow rectal measurements of Benedict and Slack. All of the latter are in the neighborhood of large blood-vessels and might be expected to rise and fall simultaneously.

All of this brings us back to the desirability of using the method of indirect calorimetry as the standard and checking its accuracy by the level of the respiratory quotient and the agreement with the direct calorimetry. All the evidence of this laboratory shows that the quotient rises and falls in regular curves in rest experiments when hourly periods are used. If, therefore, in any experiment the quotient shows a variation not accounted for by recent food, we suspect an error and usually find it compensated for in the next period. This error is almost always found in the calculation of the residual oxygen in the box at the close of the hour. Luckily there is an automatic correction in the method of calculating the indirect calorimetry. If in the first hour the oxygen estimation be too high, the quotient will be too low, and consequently the factor by which the oxygen is multiplied will be diminished. In the second hour when the error has been compensated for, the oxygen estimation will be too low, the quotient too high and the factor increased. This is another reason why the indirect calorimetry is more reliable than the oxygen consumption as an index of metabolism.

The method of direct calorimetry serves as an invaluable check, and if in any two- or three-hour experiment during which the body

temperature changes less than half a degree, the methods of indirect and direct calorimetry do not agree within 5 per cent., one should suspect a defect in the calorimeter. If in the next experiment a similar divergence be found, an alcohol check should be made and the error located. If one can prove that the error was due to any one particular determination, all calculations affected by this must be rejected as in the two experiments on F. C. G. It is by no means necessary to reject the results of the method of calorimetry not affected by the error. There is only one determination that enters into both methods of calculation, but an error in this would cause the two methods to diverge and not to err in the same direction. If through gross carelessness the first sulphuric acid bottle were allowed to gain so much weight that water vapor passed by into the $CO_2$ absorber, the direct calorimetry would be too low and the indirect too high, since both the quotient and the oxygen factor would be increased.

### DETERMINATION OF THE AVERAGE NORMAL

The selection of the proper normal base line is a matter of extreme difficulty. It is also a matter of prime importance in determining whether or not a patient or group of patients shows a total metabolism which is above or below the normal limits. In dealing with patients suffering from acute diseases it is sometimes possible to wait until the patient recovers completely and then determine his normal heat production. This is not always practicable and even when it can be done one has no guarantee that the metabolism has returned to normal unless several measurements at considerable intervals be made. In the case of patients with chronic diseases this method is out of the question. The method most commonly used is that of selecting groups of normal controls to correspond as nearly as possible to each individual patient. This of course is the ideal method if many controls be selected, but it is extremely doubtful if any investigator up to the present date has been able to gather enough satisfactory controls for each patient. The recent work of Benedict, Emmes, Roth and Smith[10] may remedy this, on account of the large number of individuals whose metabolism was determined. Even with this wealth of material one may err if allowed to pick out a small group. The individual variation is large, as one can see from a careful study of the figures. It is, perhaps, unfair to draw many deductions before the full description of the subjects is published, but we may rely on the statement that all were in presumably good health. The average heat production of the 89 men was 833 calories per square meter per day or 34.7 calories per square meter per hour. The average heat production of the 12 men studied in the bed calorimeters and grouped in Table 4 was 34.2 calories

per square meter per hour. This striking agreement is another proof that the Benedict universal respiration apparatus gives results which are almost identical with the calorimeter. For this reason the 7 subjects examined by us have for purposes of calculation been grouped with the 89 of Benedict, Emmes, Roth and Smith. In order to rule out those who were distinctly over- or underweight, the subjects were all plotted in a curve, the height forming the abscissa and the weight the ordinates. All but 9 of the subjects could be grouped between two lines not very far apart. Of the 9, W. S., O. F. M., Prof. C., H. F., F. E. M. and F. A. R. were evidently much heavier in proportion to their height than their fellows, and for this reason excluded from the averages. It is interesting to note that their average heat production was 31.5 calories per square meter. Two of the 9, R. A. C. and B. N. C., were evidently very light in proportion to their height. E. P. C. came just outside the line, but so close to it that he has not been excluded from the averages. All those over 50 years of age were arbitrarily excluded and also those under 20 years. To the remaining 72 were added the normal controls of the present paper. This process of exclusion and addition left a fairly homogeneous total of 79 whose average metabolism was 34.7 calories per square meter per hour, or exactly the same as that of the original 89 before the addition of 7 and the exclusion of 17. These 79 have been divided into four groups according to body weight in Table 4.

If we plot the heat production of all the subjects according to surface area, the range of individual variation becomes apparent. Of the total 79 we find 40 within 5 per cent. of the base line drawn at the average figure 34.7, 28 are from 5 to 10 per cent. from the average and 11 are more than 10 per cent. from the average. Of these, 6 were between 10 and 14 per cent. above, and 5 were between 10 and 15 per cent. below. This means that when we speak of a normal average we must remember a normal variation of at least 10 per cent. above and below and realize that in about 14 per cent. of the normal men the variation may be plus or minus 10 to 15 per cent. One cannot help but feel that most of the cases showing a variation of more than 10 per cent. from the average will be found to present some distinct cause for the unusual metabolism, such as an unusual degree of muscular development or muscular disuse or an unsuspected disturbance of the thyroid secretion, or the mild infection with tuberculosis which all of us pass through at some time in our lives. At any rate, one can be fairly certain that if the total heat production be 15 per cent. from the average it is distinctly abnormal, and if it be more than 10 per cent. from the average it must be regarded with great suspicion.

It may be argued that some of the variation may be due to differences in body weight. If we study the 24 normal subjects in the table we have been considering, whose weights are between 60 and 65 kg., the same variation is apparent. Of the 24, only 13 are within 5 per cent. of the average, 5 are between 5 and 12 per cent. above and 6 are from 5 to 10 per cent. below. If one investigator chanced to select this last group of 6 for his controls his average would be about 15 per cent. lower than if he selected the group of 5 cases with high metabolism. This of course is an extreme instance. It may still be argued that the factor of height must be considered. In the same table we find an exceedingly homogeneous group of 7 men whose weights are between 60.1 and 60.5 kg. and whose heights are between 171 and 175 cm. Even in this group there is a difference of 13 per cent. between the highest and the lowest and a difference of 9 per cent. between the averages of the highest 4 and the lowest 3 in this group.

This somewhat lengthy discussion is intended to show the chances of serious error in selecting any small group of normal controls to compare with a pathological case. One cannot say just how large the group should be, but it is safe to say that it must exceed 5, should exceed 10 and if possible, 50. It is obviously much better to use all the normal controls so far studied and let personal selection play no part. This can be done by basing all comparisons on the average heat production per square meter of body surface.

In Table 4 we find a comparison of the heat production calculated according to surface area and according to weight. A study of the percentage variation from the average shows clearly that all four weight groups are within 2 per cent. of the mean heat production per square meter of body surface. In other words, one can determine the average normal by this method by using a group of individuals of any weight within ordinary limits. On the other hand, the figures per kilogram of body weight show the customary diminution as weight increases and there is a difference of 16 per cent. between the heavy group and the light group. In other words, there is no such thing as an average calories per kilogram for normal men, but only a normal average for each weight. To find the normal for a given man by this method one must consult a curve. To find the normal for a given man by the method of surface area one needs only to remember the figure 34.7.

Shortly after the experimental work on the normal controls was completed it seemed advisable to investigate the accuracy of Meeh's formula and if possible devise a new formula which could be applied to individuals who depart materially from the average body form. Five subjects were measured and it was found that there was a con-

sistent plus error in Meeh's formula which, in the case of a very fat woman, amounted to 36 per cent. In two of the normal controls whose heat production had been determined, the surface area was actually measured and the errors in Meeh's formula were found to be as follows: E. F. D. B., + 14 per cent., R. H. H., + 7 per cent. In three others, G. L., F. C. G. and L. C. M., the surface area was calculated by the new formula and found to be, respectively, 14.5 per cent., 9.3 per cent. and 13.4 per cent. lower than the results obtained by Meeh's formula. Since in all four cases the new surface area figures are lower than the old results obtained from Meeh's formula, the heat production per square meter of body surface, according to the new formula, would be about 7 to 15 per cent. higher, the average being 39.9. As will be seen in the last two columns of Table 3, the new results are somewhat more uniform than the old results, but are on a higher level, and it is quite possible that it may be necessary to adopt a higher normal average than 34.7. The general principle of Meeh's formula seems to be correct for individuals of average shape, and for this reason it may be used as the standard in large groups of subjects. In the case of very fat individuals, Meeh's formula would give a figure for the calories per square meter which would be much too low. It seems probable that some of the variations from the average normal figure per square meter can be explained by the variable error in the old formula. Future use of the new formula will, it is hoped, clear up this point. The details of the new method will appear in the following paper.

There is but little evidence against Rubner's law that metabolism is proportional to surface area. As we have seen there is a plus error in Meeh's formula for determining surface area. Nevertheless, in a group of normal men of approximately average build between the weights of 45 and 85 kilograms the metabolism is, on the whole, proportional to the surface area as determined by Meeh's formula. When we come to extend Rubner's law to babies and dogs studied in the modern types of apparatus with the modern scrupulous care to exclude the effect of muscular work, we find the figure for the calories per square meter changed, yet not nearly so much changed as the figure for the calories per kilogram of body weight. Murlin and Hoobler[27] have demonstrated that in a group of infants between the ages of 2 and 12 months the metabolism is proportional to weight rather than to surface area, and have pointed out the effect of age, showing that among infants of the same age the metabolism is proportional to the

27. Murlin and Hoobler: The Energy Requirement of Normal and Marasmic Children with Special Reference to the Specific Gravity of the Child's Body, Proc. Soc. Exper. Biol. and Med., 1914, xi, 115.

surface area. Benedict and Talbot[28] believe that the metabolism of infants is not proportional to surface area, but is proportional to protoplasmic mass. Table 7 shows that comparing babies and dogs with adults the method of surface area gives results much closer to the average for men than the method of comparison by weight. It may seem superfluous at this late date to argue at length in support of Rubner's law of surface area, but this law is becoming the center of an active discussion.

The percentage of calories derived from protein in the fasting experiments is a matter of some interest in the discussion of the subject of the toxic destruction of protein. The average figures for the basal experiments on the various subjects are as follows: G. L., 16.5 per cent.; E. F. D. B., 19 per cent.; F. C. G., 18 per cent.; Louis M., 22 per cent.; John L., 15 per cent.; L. C. M., 21.5 per cent. To this list may be added the figures for several normal controls from the work of Benedict and Joslin:[29] F. G. B., 17.6 per cent.; J. R., 15.6 per cent.; J. J. C., 15.7 per cent.; D. B., 21.6 per cent.; H. F. T., 19.9 per cent.; Dr. S., 15.5 per cent.; V. G., 12.7 per cent.; T. M. C., 14.8 per cent. These figures represent largely the effect of the amount of protein in the diet of the preceding day. They are by no means the figures that would be obtained had the subjects been maintained on a protein minimum for a few days before the experiments.

### THE EFFECTS OF FOOD

The experiments on the effects of food were intended primarily as controls on the effects of similar meals given to patients with typhoid fever and exophthalmic goiter. While the subject of the specific dynamic action of food is one of great interest and importance it was felt that the chief function of the calorimeter in Bellevue Hospital was the investigation of pathological conditions. Consequently, very simple protein and carbohydrate meals which could be given in typhoid fever were the only ones studied, and the study of the effects of fat was postponed. During the season of 1913 commercial glucose containing dextrose 42.37 per cent., dextrin 44.57 per cent. and water 13.50 per cent. was used. This is one of the cheapest of food-stuffs, is readily soluble in water, is not very sweet and on account of its chemical composition should be rapidly absorbed. It has been found of great service

28. Benedict and Talbot: Studies in Respiratory Exchange of Infants, Am. Jour. Dis. Child., 1914, viii, 1; Gaseous Metabolism of Infants, Carnegie Institution of Washington, 1914, Pub. 201.

29. Benedict and Joslin: A Study of Metabolism in Severe Diabetes, Carnegie Institution of Washington, 1912, Pub. 176, p. 103.

in feeding many of the patients and in some ways is preferable to the less soluble lactose. In the season of 1914 chemically pure dextrose was used in order to compare its effects with that of the mixture. The chief protein meal used in typhoid consisted chiefly of casein in the form of cottage cheese and fat-free milk with the whites of two or three eggs and some egg yolk. It did not make a very palatable mixture, but it was consumed by most of the typhoid patients without much complaint and it certainly did them no harm. While it might have been more satisfactory to give meat, it did not seem justifiable until we had more experience with its effects in fever.

TABLE 7.—COMPARISON OF CALORIES PER KG. AND PER SQUARE METERS OF BODY SURFACE

| Investigator | Subject | Calories per Kg. | Calories per Sq. M | Per Cent. Variation from Average for Men | |
|---|---|---|---|---|---|
| | | | | According to Calories per Kg. | According to Calories per Sp.M. |
| Benedict and collaborators | 79 men | 1.08 | 34 7 | .... | .... |
| Lusk | Dog 1 | 1.65 | 31.6 | +53 | — 9 |
| Lusk | Dog 2 | 1.75 | 22.7 | +62 | — 6 |
| Lusk | Dog 3 | 1.45 | 29.8 | +35 | —14 |
| Lusk and McCrudden | Dwarf, Wt. 21.3 kg. | 1.21 | 32.3 | +12 | — 7 |
| Howland | Baby 1 | 2.80 | 39.5 | +168 | +14 |
| Howland | Baby 2 | 3.45 | 45.7 | +220 | +31 |
| Murlin and Hoobler | Average 6 infants | 2.09 | 36.3 | +150 | + 5 |
| Benedict and Talbot | Average 10 normal infants under 1 month | 1.95 | 25.6 | + 81 | —26 |
| | Average 11 normal infants between 1 and 10 months | 2.21 | 35.5 | +105 | + 2 |

Two different methods were used in obtaining a base line to represent the metabolism without food. At first the fasting metabolism was determined in the early morning and the food given while the subject was in the calorimeter. This necessitated a sojourn of three or four hours in the box after the food in addition to the two hours before the food. Even normal individuals become tired after three hours of absolute quiet in a calorimeter and it was evident that patients would be restless in such long experiments. Another disturbing factor was the gradual change in the metabolism with the different hours of the day. The method finally adopted has given great satisfaction. It is the method used so successfully by Lusk[3] on the dog. The basal metabolism is determined in a two- or three-hour experiment and two

days later the food is given before the subject is sealed in the box and the metabolism determined during the same hours studied in the fasting experiment. The basal metabolism in our experience does not change rapidly enough to make this method inaccurate. The high metabolism in the first experiment on E. F. D. B. was due to restlessness, and the low metabolism in the first experiment on F. C. G. was due to profound sleep. Between May 17, 1913, and May 18, 1914, the heat production of E. F. D. B. did not vary 3 per cent. in the three

TABLE 8.—INCREASE IN HEAT PRODUCTION FOLLOWING INGESTION OF DEXTROSE

| Subject | Hours After Glucose | Per Cent. Rise | Extra Calories | Extra Calories from Combustion of Carbohydrate | Specific Dynamic Action, Per Cent. |
|---|---|---|---|---|---|
| G. L.: 100 glucose..... | 0-1 | 20 | 15.52 | ..... | .. |
| | 1-2 | 10 | 8.16 | ..... | .. |
| | 2-3 | 3 | 2.26 | ..... | .. |
| E. F. D. B.: 100 glucose..... | 0-1 | 3 | 2.63 | 24.56 | 11 |
| | 1-2 | 11 | 8.78 | 22.38 | 39 |
| | 2-3 | 9 | 6.77 | 20.41 | 39 |
| | 3-4 | 6 | 4.28 | 23.96 | 18 |
| Total ..... | ... | .. | 22.46 | 91.31 | Av. 25 |
| E. F. D. B.: 200 glucose..... | 1-2 | 13 | 9.18 | 41.68 | 22 |
| | 2-3 | 17 | 11.73 | 37.83 | 31 |
| | 3-4 | 8 | 5.98 | 39.22 | 15 |
| | 4-5 | 7 | 5.12 | 40.08 | 13 |
| Total ..... | ... | .. | 32.01 | 158.81 | Av. 20 |
| L. C. M.: 200 glucose..... | 1-2 | 24 | 15.09 | 33.37 | 45 |
| | 2-3 | 16 | 10.49 | 41.04 | 26 |
| | 3-4 | 16 | 10.25 | 40.85 | 25 |
| Total ..... | ... | .. | 35.83 | 115.26 | Av. 31 |

tests made. In some of the ward patients studied the metabolism has remained constant from day to day and even in typhoid fever has changed in gradual curves. Two hundred grams of dextrose or its equivalent caused an average increase of 12.5 per cent. in the first three to six hours after its ingestion. One hundred grams caused an average increase of 9 per cent. The casein meal with 10.5 gm. N increased the metabolism 12 per cent., the beef with almost 24 gm. nitrogen increased

it 22 per cent.* A more detailed study of the effects of food is given in Tables 8 and 9, which show the effects in the different periods. The percentage increase in metabolism and the extra calories produced are calculated from the nearest basal determination. The extra protein calories produced are calculated from the increase in the urine nitrogen above the average hourly elimination of the nearest basal determination. The extra grams of urinary nitrogen when multiplied by the factor 26.51 give the extra calories from the combustion of protein during that hour. The extra calories produced when divided by this

TABLE 9.—INCREASE IN HEAT PRODUCTION FOLLOWING PROTEIN MEAL

| Time After Protein Meal, Hours | Per Cent. Rise in Metabolism | Extra Calories Produced | Extra Protein Calories Metabolized. Extra Urine N × 26.51 | Specific Dynamic Action, Per Cent. |
|---|---|---|---|---|
| E. F. D. B.: 10.5 N | | | | |
| 1½ to 2½ | 8.0 | 5.93 | 8.96 | 60 |
| 2½ to 3½ | 16.5 | 12.34 | 8.27 | 140 |
| 3½ to 4½ | 12.1 | 9.03 | 10.13 | 90 |
| 4½ to 5½ | 15.5 | 11.54 | 1.56 | 738 |
| 5½ to 6½ | 6.8 | 5.04 | 1.56 | 300 |
| Total | .... | 43.88 | 30.48 | Av. 144 |
| Louis M.: After 23.93 N | | | | |
| 2 to 3 | 15.1 | 9.68 | 4.80 | 203 |
| 3 to 4 | 16.2 | 10.36 | 4.59 | 225 |
| 4 to 5 | 28.0 | 17.94 | 11.88 | 151 |
| 5 to 6 | 27.5 | 17.62 | 13.04 | 135 |
| 6 to 7 | 17.6 | 11.30 | 16.33 | 69 |
| 7 to 8 | 25.7 | 16.45 | 15.64 | 106 |
| Total | .... | 83.35 | 66.28 | Av. 126 |

figure for the extra protein calories metabolized, give the specific dynamic action in the sense of Rubner (see Note 2, Williams, Riche and Lusk, p. 370), amounting to as much as 144 per cent. and 126 per cent. for the two experiments. The accuracy of this method of calculation may be impaired by the lag in the excretion of nitrogen by

* Since the completion of this paper two more normal men have been given the test meals. Morris S. on Dec. 18, 1914, showed a rise of 6.5 per cent. after a meal containing 9.6 gm. nitrogen. Albert G. on Jan. 6, 1915, showed an increase of 9 per cent. in his metabolism after 115 gm. commercial glucose (100 gm. dry glucose).

the kidneys. In the dextrose experiments the method of calculation is slightly different from the method used by Lusk.[2] The extra calories produced by the combustion of carbohydrate are reckoned as follows: In the nearest basal determination the average figure for the calories per hour is multiplied by the percentage of calories furnished by the combustion of carbohydrate. A similar calculation is made in each hour of the experiment in which dextrose was administered and the extra carbohydrate calories metabolized in each hour determined. This figure divided into the extra calories produced gives the specific dynamic action of 25, 20 and 31 per cent. in the three experiments.

## SUMMARY AND CONCLUSIONS

Seven normal men were studied with and without food as controls for the observations on patients in the metabolism ward. Their average basal metabolism (at perfect rest, fourteen to eighteen hours after their last meal) was 34.8 calories per hour per square meter of body surface. The average basal metabolism of 89 normal men studied by Benedict, Emmes, Roth and Smith[10] was 34.7 calories. The average of the 7 men studied in the Sage bed calorimeter in Bellevue and of the 5 men studied in Benedict's bed calorimeter in Boston was 34.2 calories. As a result we have adopted the figure of 34.7 calories per square meter of the body surface as the average heat production of normal men between the ages of 20 and 50 years.

All of the subjects studied in the bed calorimeter were within 11 per cent. of this average. Of the 79 men of normal figure between the ages of 20 and 50 studied by Benedict and collaborators, 86 per cent. were within 10 per cent. of the average and the remainder between 11 and 15 per cent. If, therefore, the heat production of a given subject suffering from some pathological condition is more than 10 per cent. above or below the average it may be regarded as abnormal, but cannot be proved abnormal unless the departure from the average is at least 15 per cent.

Groups of men of weights between 45 and 85 kilograms show a mean heat production within 2 per cent. of the average according to surface area. According to calories per kilogram of body weight the group weighing between 75 and 85 kg. produces 7 per cent. less than the average figure and the group between 45 and 55 kg. produces 9 per cent. more than the average. The conclusion is therefore drawn that among groups of men of varying weights metabolism is proportional to surface area according to Rubner's law and is not proportional to body weight. By using the surface area as a basis one can refer all individuals to a single average normal figure, 34.7. If one uses the body weight as a basis a different normal figure is required for each weight.

The methods of direct and indirect calorimetry in disease agree in two- and three-hour periods; and in health may be found to agree in hourly periods. In the total measurement of 4,577 calories in the experiments reported in this paper the two methods have agreed within 0.17 per cent. In a total of thirty one-hour periods on one normal subject the two methods have agreed within 5 per cent. in twenty-one individual hours and within 10 per cent. in twenty-seven of the periods.

The method of indirect calorimetry using the oxygen consumption as a basis gives the best results in hourly periods. The method of direct calorimetry in short periods is made difficult by uncertainty as to the correct specific heat of the body and also by the fact that the different parts of the body do not always change their temperatures at the same rate. On the average one obtains the best results by considering that the rectal temperature change indicates the mean temperature change of the body, but in typhoid fever the surface thermometers often give a better indication of the mean body change.

The most satisfactory method of determining the effect of food in increasing heat production in normal subjects and patients is to determine the basal metabolism at frequent intervals, and on days shortly after a basal determination administer the food before the subject is sealed in the calorimeter. It has been found that 200 gm. of dextrose or its equivalent in commercial glucose or a casein meal with 10.5 gm. of nitrogen increase the heat production by about 12 per cent. over a period of three to six hours. The basal metabolism of patients with various diseases and the effects of this same food will be discussed in subsequent publications.

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# CLINICAL CALORIMETRY

FIFTH PAPER

## THE MEASUREMENT OF THE SURFACE AREA OF MAN*

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Recent work on the basal metabolism of infants and adults has revived interest in Rubner's law that heat production in different individuals and species of animals is proportional to the surface area. This law was first definitely formulated by Rubner[1] in 1883, although suggested by Bergman[2] many years before. At the time the experimental work in support of this theory was done no record was kept of body movements and men and animals were allowed to move during the periods of investigation. The average heat production per square meter of body surface was about 1,000 calories per day. In modern work, where the influence of muscular activity is absolutely excluded, the figure is in the neighborhood of 830 calories per square meter per day, as has been shown in Paper 4 of this series. With these new figures it is not unnatural that many investigators have felt that the whole question must be studied anew. Very recently Murlin and Hoobler[3] in New York and Benedict and Talbot[4] in Boston have all concluded that among infants metabolism is more nearly proportional to body weight than to surface area. If this is true for adults, it is a matter of great theoretical and practical importance.

It is obvious that the whole question rests on the accuracy of the determinations of the basal metabolism and of the surface area. The methods of determining the metabolism have been greatly improved, leaving the surface area the doubtful factor. The number of formulas for surface area determination is large, the number of individuals

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* From the Russell Sage Institute of Pathology, in affiliation with the Second Medical Division of Bellevue Hospital.

1. Rubner: Ueber den Einfluss der Körpergrosse auf Stoff- und Kraftwechsel, Ztschr. f. Biol., 1883, xix, 545.

2. Bergman: Wärmeökonomie der Thiere, Göttingen, 1848, p. 9.

3. Murlin and Hoobler: The Energy Metabolism of Normal and Marasmic Children with Special Reference to the Specific Gravity of the Child's Body, Proc. Soc. Exper. Biol. and Med., 1914, xi, 115.

4. Benedict and Talbot: Studies in the Respiratory Exchange of Infants, Am. Jour. Dis. Child., 1914, viii, 1; The Gaseous Metabolism of Infants, Carnegie Institution of Washington, 1914, Pub. 201.

whose area has been measured is small. In 1879 Meeh[5] finished his painstaking and time-consuming work which has remained the standard ever since. He measured six adults and ten children, using a variety of methods. Some parts of the body were marked out in geometrical patterns, which were then traced on transparent paper. The areas of these were then determined by geometry, or, if the pieces of paper were very irregular, by weighing. Some of the cylindrical parts of the body were wound with strips of millimeter paper like a bandage. Funke[6] in one case covered the skin of a cadaver with adhesive material and pasted over this squares of paper. Fubini and Ronchi[7] measured one man by marking out the anatomical regions of the body and determining the areas geometrically. Bouchard[8] used this same method in measuring a number of adults. He speaks of a plan of clothing the body in tights made of some thin, flexible, inelastic sort of paper, the area of which could be determined by weighing. Apparently, he was not able to find the right material. He mentions the fact that M. Bergonie measured surface area by means of plates of lead, and that M. Roussy used a very ingenious cylinder with a revolution counter which he passed over the whole surface of the body. Bouchard also states that D'Arsonval determined the surface area electrically by clothing the man in silk tights and charging him as one would charge a Leyden jar, calculating the surface by applying a metal plate of known area. Lissauer[9] measured twelve dead babies by covering the skin with colored adhesive material and then applying silk paper and measuring the area of the paper geometrically or with a planimeter.

Meeh[5] as a result of his own measurements, based his formula for determining surface area on the fundamental mathematical law that the surfaces of similar solids are proportional to the $\frac{2}{3}$ power of their volumes. Using the body weight to represent volume he determined that the constant 12.312 when multiplied by the cube root of the square of the weight in kilograms gave results which came within 7 per cent. of all his measurements of adults and older children. The constant for infants was 11.9 and for various species of animals still different. Miwa and Stöltzner[10] felt the need of introducing linear measurements

5. Meeh: Oberflächenmessungen des menschlichen Körpers, Ztschr. f. Biol., 1879, xv, 425.

6. Funke: Moleschott's Untersuchungen, z. Naturlehre, 1858, iv, 36.

7. Fubini and Ronchi: Ueber die Perspiration der $CO_2$ beim Menschen Moleschott's Untersuchungen, z. Naturlehre, 1881, xii.

8. Bouchard, Ch.: Traité de Pathologie générale, Paris, 1900, iii[2], 200, 384.

9. Lissauer, W.: Ueber Oberflächenmessungen an Säuglingen und ihre Bedeutung für den Nahrungsbedarf, Jahrb. f. Kinderh., 1902, lviii, 392.

10. Miwa and Stöltzner: Bestimmung der Körperoberfläche des Menschen, Ztschr. f. Biol., 1898, xxxvi, 314.

and chose the height (L) and the circumference of the chest (U) at the level of the nipples in men and just above the breasts in women, retaining the weight (G) as a factor. Using Meeh's measurements they determined by means of the following formula,

$$\text{Surface} = \frac{\text{K UGL}}{\sqrt[4]{\text{G}^2\text{L}^2\text{U}^2}} \text{ using an average constant (K) of 4.5335.}$$

This formula, which might have been simplified to $\text{Surface} = \text{K}\sqrt[3]{\text{U}^2\text{GL}}$ has never been much used, although its originators have shown that it comes closer to Meeh's cases than Meeh's own formula. Lissauer from the measurement of babies, almost all of whom were atrophic, retained the principles of Meeh's formula, but found that the constant 10.3 gave better results than the constant 11.9. This indicated that Meeh's figure was about 16 per cent. too high. The formula of Miwa and Stöltzner, according to Lissauer, gave no better results than that of Meeh. Howland and Dana,[11] using the measurements of Meeh and Lissauer, have devised a simple formula in which the surface area (y) of the child equals the weight in grams (x) multiplied by a constant 0.483 (m) plus 730 (b). This is expressed in the terms $y = mx + b$.

Bouchard found a consistent plus error in Meeh's formula as given in Table 1. In his own formula, which requires twenty-five pages of tables for its application, he uses the body weight, the height and the diagonal circumference of the abdomen from the hollow of the back to a point somewhere above the umbilicus according to the degree of obesity. Bouchard states that a measuring tape passed around the abdomen and moved back and forth will of itself find the right circumference, which he calls the "tour de taille." Bouchard's formula has been very little used, as it seems to be difficult to understand and apply.

Recently Dreyer, Ray and Walker[12] have made many measurements of birds and small mammals and have found that the surface area, blood volume, cross sections of the aorta and trachea are all nearly proportional to the ⅔ power of the weight. The formula which applies to all these measurements is $S = k W^n$, in which S is the surface, blood volume, etc.; k is a constant which varies with the species; W is the weight, and n is approximately 0.70-0.72 instead of 0.666 which would be the ⅔ power. Benedict and Talbot[4] have suggested that the active mass of protoplasmic tissue develops normally on this ratio. They are convinced that metabolism is determined, not by the body

11. Howland and Dana: A Formula for the Determination of the Surface Area of Infants, Am. Jour. Dis. Child., 1913, vi, 33.

12. Dreyer and Ray: Phil. Trans., 1909-10, cci, Series B, p. 133. Dreyer, Ray and Walker: The Size of the Aorta in Warm-Blooded Animals and its Relationship to Body Weight and to Surface Area, Expressed in a Formula, Proc. Roy. Soc., 1912-1913, lxxxvi, Series B, pp. 39 and 56.

surface, but by the active mass of protoplasmic tissue. If both are assumed proportional to the same thing, it will be a difficult matter to prove which is the more important factor.

As shown in Paper 4 of this series, the metabolism of the normal and pathological subjects studied in the Sage respiration calorimeter in Bellevue Hospital has been expressed in terms of calories per square

TABLE 1.—Determination of Error in Meeh's Formula as Applied to Measured Individuals

| Subject | Observer | Weight, Kg. | Surface Area as Measured, Sq. Cm. | Constant for Meeh's Formula, Area Divided by Wt.$^{2/3}$ | Error in Meeh's Formula | Age, Yrs. | Height, Cm. | Body Form |
|---|---|---|---|---|---|---|---|---|
| Benny L. ..... | D.B. and D.B. ..... | 24.2 | 8,473 | 10.13 | +21 | 36 | 110.3 | Cretin. Short and fat. |
| Hagenlocher .... | Meeh..... | 28.30 | 11,883 | 12.80 | — 4 | 13.1 | 137.5 | Medium strong. |
| Very thin woman | Bouchard..... | 31.8 | 12,737 | 12.69 | — 3 | ... | .... | Very thin. |
| Korner ..... | Meeh..... | 35.38 | 14,988 | 13.17 | — 7 | 15.7 | 152 | Muscular. |
| Schneck ..... | Meeh..... | 50.00 | 17,415 | 12.96 | — 5 | 36 | 158 | Very thin. |
| Adult man ..... | Fobini and Ronchi | 50.00 | 16,067 | 11.84 | + 4 | ... | .... | ? |
| Nagel ..... | Meeh..... | 51.75 | 18,158 | 12.96 | — 5 | 45 | 160 | Somewhat thin. |
| Fr. Brotbeck ... | Meeh..... | 55.75 | 19,206 | 13.16 | — 6 | 17.7 | 169 | Very strong and muscular. |
| Naser ..... | Meeh..... | 59.50 | 18,695 | 12.27 | + 0 | ... | 170 | Somewhat thin, but well proportioned. |
| Normal man .... | Bouchard..... | 61.6 | 18,950 | 12.13 | + 2 | ... | .... | Normal man. |
| Fr. Haug ..... | Meeh..... | 62.25 | 19,204 | 12.01 | + 2 | 26.2 | 162 | Strong. |
| Morris S. ..... | D.B. and D.B. ..... | 64.0 | 16,720 | 10.45 | +17 | 21 | 164.3 | Short and rather stout. |
| R. H. H. ..... | D.B. and D.B. ..... | 64.08 | 18,375 | 11.49 | + 7 | 22 | 178 | Tall and thin. |
| Forstbauer ..... | Meeh..... | 65.50 | 20,172 | 12.48 | — 1 | 66 | 172 | Still very strong. |
| E. F. D. B. ..... | D.B. and D.B. ..... | 74.05 | 19,000 | 10.55 | +14 | 32 | 179.2 | Tall, average build. |
| Normal woman.. | Bouchard..... | 76.5 | 19,484 | 10.81 | +14 | ... | .... | Normal woman. |
| Kehrer ..... | Meeh..... | 78.25 | 22,435 | 12.26 | + 0 | 36 | 171 | Corpulent. |
| Large man ..... | Bouchard..... | 88.6 | 21,925 | 11.03 | +12 | ... | .... | Large strong man. |
| Mrs. McK. ..... | D.B. and D.B. ..... | 93.0 | 18,592 | 9.06 | +36 | ... | 149.7 | Very short and very fat. |
| Very fat man... | Bouchard..... | 140.0 | 24,966 | 9.26 | +33 | ... | .... | Very fat man. |

meter per hour. The work had progressed but a short distance when it was obvious that no formula based on weight could give the surface area of all the patients with any great degree of accuracy. Among the patients studied were men emaciated from typhoid fever and hyperthyroidism, men of normal shape and men with acromegaluy, hypophysial dystrophy and cretinism. Eventually, it is hoped every conceivable shape will be studied. A formula such as Meeh's is accurate only for objects of different size, *but of similar shape.*

The obvious method for determining surface area is to multiply the length by the average width. An attempt has been made to measure a characteristic length and an average or characteristic circumference of each part of the body and determine the area of the part by multiplying the two and correcting by a constant factor. The sum of the parts will then give the total surface area of the body. When the proper measurements have been selected and the constants for each part determined, it is evident that the method can be applied to individuals of varying shape no matter what disproportion may exist between the different parts of the body.

Fig. 16.—The cretin, Benny L., with mold of his surface area.

### INDIVIDUALS MEASURED

The five individuals whose surface area was measured differed from each other in bodily form to a marked degree. All of them had served as the subjects of observations in which the basal metabolism was determined. Benny L. was a cretin 36 years old with the general mental and physical development of a boy of 8. As his photograph (Fig. 16) shows, he was short and stocky, with prominent abdomen, short thick extremities and rather small head. Morris S., 21 years old, was measured three months after he was discharged from the hospital, where he

had been confined three and one-half months with a severe attack of typhoid fever. He had recovered even more than his usual weight in the hospital and during the subsequent stay in the country. At the time he was measured he was of well rounded figure, almost stout. He was short and of small frame, with small hands and feet. R. H. H., a chemist, 22 years old, was tall and thin, with long, slim bones, sinewy muscles and very little subcutaneous fat. E. F. D. B., 32 years old, was tall, but of average build. Mrs. McK. was a very short and very fat woman whose metabolism had been studied in great detail by Dr. David

TABLE 2.—MEASUREMENTS USED IN FORMULA

| Index Letter of Part Measured | Benny L. | Morris S. | R. H. H. | E. F. D. B. | Mrs. McK. |
|---|---|---|---|---|---|
| A | 57.5 | 63.9 | 65.0 | 67.0 | 58.0 |
| B | 50.2 | 54.1 | 56.6 | 57.8 | 56.6 |
| F | 37.2 | 56.7 | 65.0 | 67.3 | 55.0 |
| G | 20.2 | 29.5 | 27.5 | 32.5 | 33.0 |
| H | 18.7 | 24.6 | 26.0 | 27.5 | 27.0 |
| I | 12.8 | 16.7 | 16.3 | 16.2 | 16.5 |
| J | 13.6 | 20.0 | 21.5 | 20.2 | 17.0 |
| K | 15.2 | 20.4 | 20.5 | 20.5 | 17.5 |
| L | 36.6 | 55.0 | 55.0 | 51.5 | 56.0 |
| M | 62.0 | 76.2 | 72.5 | 77.0 | 111.0 |
| N | 63.5 | 87.2 | 85.8 | 96.0 | 100.0 |
| O | 26.4 | 41.7 | 47.0 | 46.3 | 40.0 |
| P | 35.5 | 55.5 | 54.0 | 59.0 | 60.0 |
| Q | 61.0 | 96.0 | 93.2 | 96.5 | 117.0 |
| R | 29.3 | 41.7 | 47.0 | 49.4 | 36.8 |
| S | 23.7 | 35.7 | 33.8 | 37.0 | 41.0 |
| T | 17.7 | 24.8 | 26.2 | 28.3 | 21.5 |
| U | 16.8 | 22.5 | 22.2 | 23.5 | 19.3 |
| V | 15.7 | 21.2 | 21.2 | 23.5 | 22.0 |

Edsall and Dr. James H. Means in Boston. We are greatly indebted to Dr. Means for taking the measurements of this subject and for taking the mold of the surface and sending it to us to be measured.

### MEASUREMENTS OF THE BODY

The individual to be measured was undressed, weighed and placed on a flat table with a vertical foot-board about 30 cm. high. All the measurements were made with the subject flat on his back with his feet against the foot-board. A steel tape was used for all the linear meas-

urements and a cloth tape for the circumferences. The measurements actually used are given in Table 2; those not used are given in Table 3 in case other investigators wish to apply different formulas.

### THE MOLD OF THE BODY

The method of determining the surface area finally adopted consisted in making a thin mold of the body, cutting this up in pieces which would lie flat, printing the patterns of these pieces on photo-

TABLE 3.—MEASUREMENTS NOT USED IN FORMULA

| Index Number of Part Measured | Benny L. | Morris S. | R. H. H. | E. F. D. B. | Mrs. McK. |
|---|---|---|---|---|---|
| I | 24.2 kg. | 64.0 kg. | 64.08 | 74.49 | 93.0 |
| II | 110.5 cm. | 164.3 cm. | 178.0 | 179.2 | 149.7 |
| III | 88.3 | 135.5 | 148.0 | 147.2 | 125.0 |
| IV | 81.1 | 124.6 | 136.5 | 135.5 | ..... |
| V | 83.6 | 124.4 | 139.0 | 141.2 | 125.4 |
| VI | 76.5 | 115.2 | 130.0 | 125.5 | 107.0 |
| VII | 55.7 | 83.4 | 94.0 | 95.7 | 76.8 |
| VIII | 46.2 | 72.3 | 84.5 | 85.5 | 60.2 |
| IX | 65.1 | 82.5 | 80.7 | 84.5 | 92.0 |
| X | 40.0 | 60.2 | 81.5 | 67.5 | 55.5 |
| XI | 29.6 | 43.6 | 48.0 | 49.0 | 40.0 |
| XII | 8.2 | 11.3 | ..... | 11.7 | 15.8 |
| XIII | 17.0 | 24.5 | 27.0 | 28.0 | 21.0 |
| XIV | 21.2 | 33.1 | 38.5 | 38.5 | 32.0 |
| XV | 18.6 | 27.5 | 25.2 | 30.0 | 30.5 |
| XVI | 17.8 | 26.0 | 25.0 | 29.0 | 30.0 |
| XVII | 35.5 | 50.3 | 48.0 | 56.5 | 56.0 |
| XVIII | 23.2 | 34.7 | 32.7 | 37.5 | 39.0 |
| XIX | 22.6 | 31.0 | 31.5 | 33.5 | 30.6 |
| XX | 43.2 | 52.0 | 48.0 | 52.5 | 35.5 |
| XXI | 28.5 | 36.0 | 36.0 | 37.0 | 24.2 |
| XXII | 74.5 | 108.0 | 90.0 | 107.0 | 106.0 |

graphic paper (Fig. 17) and finding the area of the printed patterns by cutting them out and weighing them. The subject was dressed in a tight-fitting suit of thin union underwear, which covered the body, arms and legs. Socks were put on the feet, thin cotton gloves on the hands, while over the head and neck was slipped a section of the leg of a knitted undersuit held in place by means of bandages. On this groundwork strips of paper were pasted until a flexible inelastic mold of the

body was completed. The material used was strong manila paper, about 1½ inches broad, gummed on one side. It is manufactured in large rolls and is used by stores as a substitute for string in doing up small packages and also by some tailors in making models of their customers. For our purposes it was wound in small rolls and placed in a small brass holder which moistened the gummed side as it was applied to the cloth covering the body. It could be applied so quickly that very little

Fig. 17.—Reduced photograph of the patterns printed from the mold of the head and neck of one of the subjects measured. The patterns of the head marked with one punch were cut out and weighed separately from the pieces of the neck marked with two punches. The dark areas were also weighed as control.

time was required to cover the body. The head presented no difficulty until the nose was reached. This region was the last to which the paper was applied and a couple of holes were left for the person to breathe through. The mold of the face was then quickly opened by means of curved bandage scissors. In most cases only one arm and one leg were measured.

TABLE 4.—Comparison of Areas of Parts of Body as Actually Measured and as Calculated from Formulas

| Part of Body | Benny L | | | Morris S. | | | R. H. H. | | | E. F. D. B. | | | Mrs. McK. | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Area as Measured, Sq. Cm. | Area as Calculated from Formula, Sq. Cm. | Error in Formula, Per Cent. | Area as Measured, Sq. Cm. | Area as Calculated from Formula, Sq. Cm. | Error in Formula, Per Cent. | Area as Measured, Sq. Cm. | Area as Calculated from Formula, Sq. Cm. | Error in Formula, Per Cent. | Area as Measured, Sq. Cm. | Area as Calculated from Formula, Sq. Cm. | Error in Formula, Per Cent. | Area as Measured, Sq. Cm. | Area as Calculated from Formula, Sq. Cm. | Error in Formula, Per Cent. |
| Head..... | 900 | 886 | — 1 | 1,030 | 1,064 | +3 | 1,173 | 1,122 | —4 | 1,154 | 1,192 | +4 | 1,090 | 1,010 | — 7 |
| Arms..... | 1,092 | 1,074 | — 2 | 2,314 | 2,236 | —3 | 2,524 | 2,535 | +0 | 2,776 | 2,865 | +3 | 2,298 | 2,351 | + 2 |
| Hands..... | 596 | 458 | —23* | 900 | 905 | +1 | 968 | 977 | +1 | 876 | 918 | +5 | 678 | 660 | — 3 |
| Trunk..... | 3,060 | 3,229 | + 6 | 6,304 | 6,318 | +0 | 6,444 | 6,121 | —5 | 6,572 | 6,264 | —5 | 7,746 | 8,308 | + 7 |
| Thighs..... | 1,284 | 1,294 | + 1 | 3,022 | 3,207 | +6 | 3,712 | 3,512 | —5 | 3,820 | 3,655 | —4 | 3,500 | 3,594 | + 3 |
| Legs..... | 930 | 973 | + 5 | 2,000 | 2,085 | +4 | 2,396 | 2,225 | —7 | 2,472 | 2,560 | +4 | 2,156 | 2,112 | — 2 |
| Feet..... | 611 | 596 | — 2 | 1,150 | 1,123 | —3 | 1,158 | 1,178 | +2 | 1,330 | 1,378 | +4 | 1,124 | 930 | —18 |
| Total..... | 8,473 | 8,512 | + 0.5 | 16,720 | 16,938 | +1.3 | 18,375 | 17,680 | —3.8 | 19,000 | 18,832 | +0.9 | 18,592 | 18,956 | + 2.0 |

* Benny L. had chronic ulcers on his hands, and the measurement was made with difficulty. The hands of six other individuals were measured and calculated by the formula. The percentage of errors of the calculations in these cases were: —4.0, —1.8, +2.5, —1.8, +2.0 and —2.7.

The hands could not be covered satisfactorily with paper, and hard paraffin was used instead. This was melted and applied to the glove with a brush, soaking well into the meshes of the cotton. The melted paraffin was not too warm for the hands, but was uncomfortable for parts of the body which were not so accustomed to heat. Starch was tried in some instances, but dried too slowly; plaster-of-Paris was too stiff.

Certain portions of the skin were not measured by this mold. The area back of the ears was determined by tracing the back of the ears on a piece of cardboard and correcting by careful measurements. The skin between the toes was measured by tracing. The penis and scrotum were measured and the area determined geometrically. This left unmeasured only very small portions of the face and ears since the mold did not fit closely into the eye-sockets and the concavities of the ear. This error could not have amounted to more than 10 to 20 square centimeters in a total of fifteen thousand.

While the mold was still on the subject the landmarks of the body were located through the paper and the different anatomical regions marked off by drawing the borders on the paper. The mold was then removed with bandage scissors or small probe pointed scissors and the inside of the cloth covered with a thin layer of melted paraffin which, when it hardened, left a material much easier to work with than the cloth and paper alone, since this would not lie flat. Next the mold was cut at the borders of the various regions of the body and each of these regions cut into pieces which would lie flat. These pieces were then marked with a punch for identification and transferred to a large photographic printing frame. After printing in the sun and without developing or fixing, patterns of the pieces of the mold were cut out and weighed to the tenth of a milligram and the blank parts of the sheet weighed as a control. Before this printing each sheet of photographic paper was carefully measured and weighed and the area of each gram of paper determined. By weighing the patterns of each region together it was a simple matter to find the area of that region. A copy of the print made from the mold of the head and neck of one of the subjects is given in Figure 17 showing the method of cutting the paraffined mold so that it would lie flat.

### ACCURACY OF METHOD

The accuracy of the procedure was tested in several ways. The bottom of a porcelain evaporating dish was measured twice with a difference of 0.1 per cent. between the two measurements. The surface of the hand of D.D.B. was measured three times, the glove being covered once with starch and on the two other occasions with paraffin.

The square centimeters of surface area as determined on the three occasions were 555.5, 556.0 and 555.5. The right and left sides of the whole body of Benny L. measured separately, agreed within 0.5 per cent.

### MEASUREMENTS

The body was divided into the larger regions used by Meeh. An effort was made to select the measurements which represented the length and average breadth of the part. The head region included the ears and the trunk included the neck, the breasts in the female, and the penis and scrotum in the male.

### DETERMINATION OF NEW FORMULA

Having measured the surface areas of the different parts of the body and the linear measurements of these parts, the formula to determine the surface area of each part was calculated as follows: the various measurements of length were multiplied by various sums of the measurements representing the width; the resulting figure was divided by the surface area as actually measured. The factors resulting from this calculation in each of the five individuals were compared to determine the percentage variation. That particular combination of length and breadth measurements which showed the smallest variation was chosen and the reciprocal of the average factor for this combination taken as a constant. Fortunately the best results were always obtained by using measurements which were simple. The factors include the multiplication by two necessary to give the area of the right and left arm, hand, etc.

### MEASUREMENTS USED IN FORMULA (TABLE 2).

HEAD: AB 0.308.
- A—Around vertex and chin.
- B—Around occiput and forehead, just above eyebrows.

ARMS: F(G + H + 1) 0.558.
- F—Outer end of clavicle to lower border of radius.
- G—Circumference at level of upper border of axilla.
- H—Largest circumference of forearm.
- I—Smallest circumference of wrist.

HANDS: JK 2.22.
- J—Lower posterior border of radius to tip of second finger.
- K—Circumference of open hand.

TRUNK: L(M + N) 0.703.
- L—Suprasternal notch to upper border of pubes.
- M—Circumference of abdomen at level of umbilicus.
- N—Circumference of thorax at level of nipples in the male, and just above breasts in the female.

THIGHS: O(P + Q) 0.508.
- O—Superior border of the great trochanter to the lower border of the patella.
- P—Circumference of thigh just below the level of the perineum.
- Q—Circumference of hips and buttocks at level of trochanters.

LEGS: *RS* 1.40.
R—From sole of foot to lower border of patella.
S—Circumference at level of lower border of patella.

FEET: T(U + V) 1.04.
T—Length of Foot.
U—Circumference of foot at base of little toe.
V—Smallest circumference of ankle.

MEASUREMENTS NOT USED IN FORMULA (TABLE 3)

I—Weight.
II—Height.
III—Sole of foot to suprasternal notch.
IV—Sole of foot to level of nipples.
V—Sole of foot to upper border of axilla.
VI—Sole of foot to tip of ensiform process.
VII—Sole of foot to superior border of great trochanter.
VIII—Sole of foot to perineum.
IX—Circumference of body at level of tip of ensiform.
X—Tip of second finger to upper border of axilla.
XI—Tip of second finger to tip of olecranon process.
XII—Tip of second finger to metacarpo-phalangeal joint.
XIII—Tip of olecranon to lower border of radius.
XIV—Tip of olecranon to outer end of clavicle.
XV—Circumference of arm at the insertion of the deltoid.
XVI—Circumference of arm at belly of biceps.
XVII—Circumference of thigh half way between anterior superior spine of the ilium and the lower border of the patella.
XVIII—Largest circumference of calf.
XIX—Circumference of foot around heel.
XX—From back of neck around superior maxilla just below ears and nose.
XXI—Around neck just below larynx.
XXII—Around shoulders at level of heads of humeri.

BORDERS OF REGIONS OF BODY:
Head: Lower margin of the mandible to its posterior border, thence to tip of the mastoid process and in a straight line to the external occipital protuberance.
Arm: From the acromion process anteriorly and posteriorly to the upper border of the axilla.
Hand: Line at right angles to long axis of forearm drawn at level of tip of ulna.
Thigh: From the perineal point going posteriorly in the natal fold to the upper border of the great trochanter, thence medially in a straight line to the perineal point.
Leg: Line at level of lower border of patella.
Foot: Line at level of tip of lateral malleolus.

## DISCUSSION OF RESULTS

Table 1 shows that the constant employed by Meeh has not been confirmed by subsequent observers. It gives results which are too high in every case except one very thin woman. Lissauer found Meeh's figure for infants 16 per cent. too high. Bouchard in four of his five cases found it from 2 to 33 per cent. too high, while in our five cases we have found it from 7 to 36 per cent. too high. The majority of Meeh's

subjects seem to have been thin, and the error of the formula is very great in fat individuals. One can perhaps obtain fairly accurate results in using Meeh's formula if one retains the factor of 12.3 for thin subjects, 11 to 12 for people of average build, 10 to 11 for the moderately stout and 9 to 10 for the very fat. Possibly at some later date a more accurate factor can be determined by the relationship of weight to height, retaining Meeh's fundamental principle of the ⅔ power of the weight.

Miwa and Stöltzner's formula gives results only slightly better than Meeh's. The errors in calculated areas of our five subjects using their formula are as follows: Benny L. + 18 per cent., Morris S. + 17 per cent., R. H. H. + 8 per cent., E. F. D.B. + 18.5 per cent., Mrs. McK. + 26.5 per cent. If the constant of 3.84 were used instead of 4.5335 the results would be much better for this series.

The series of five individuals measured by us is perhaps too small to determine factors which will remain unaltered by subsequent research, but it is doubtful if the changes will be of significance. The range of body shape among our subjects was, however, very great, and the error of the factors comparatively small. The principle of the method has been demonstrated to be sound. Unfortunately, it involves the taking of nineteen measurements, a matter of perhaps fifteen minutes time. Subsequent investigation may reduce the number, but it is difficult to see how one can avoid measuring each part of the body if one wishes to obtain accurate results on people whose shapes do not correspond closely to the average.

In any discussion as to whether metabolism is proportional to body weight or to surface area it is essential to apply a method of measuring the surface which does not depend entirely on weight. The key to the question may perhaps be found in those individuals whose surface area is not proportional to the ⅔ power of their weight, multiplied by a constant determined by measurements of average individuals.

## SUMMARY AND CONCLUSIONS

The discussion of the relationship of metabolism to surface area has been based almost entirely on Meeh's formula as determined in 1879. Subsequent observers have found a consistent plus error in this formula amounting to as much as 36 per cent. in the case of very fat individuals.

The surface area of the various parts of the body can be determined as follows: A mold of the surface is made by pasting paper over tight-fitting underwear. The area of the mold is then determined by cutting it in pieces, printing a pattern on photographic paper, cutting out the pieces of the pattern and weighing them.

To determine the area of each part of the body by linear measurements alone a formula has been devised on the principle of length times the average breadth times a constant. The sum of these parts gives the total surface area of the body.

Five individuals of widely varying shapes have been measured and the surface area as calculated from the formulas compared with the surface area as actually measured. In the five cases the average error was 1.7 per cent.

In discussing the question as to whether the basal metabolism is proportional to surface area or to weight it is preferable to determine the surface area by a formula which is not of necessity a function of the weight.

NOTE.—Since this article was submitted for publication the formula has been tested on a tall and exceedingly thin boy, 18 years old. This patient, Gerald S., came to the hospital much emaciated from diabetes and was kept for eleven days practically without food, receiving only whisky. The mold of the body was taken on Dec. 1, 1914, shortly after his fast. At this time he weighed 45.25 kg. His surface area according to Meeh's formula was 1.563 square meters. The mold was kindly measured for us by Miss Margaret Sawyer who obtained the following figures:

| | Actual Area as Measured sq. cm. | Area as Calculated from Formula sq. cm. | Error in Formula Per Cent. |
|---|---|---|---|
| Head | 950 | 978 | + 3 |
| Arms | 2,052 | 2,047 | — 0 |
| Hands | 847 | 875 | — 0 |
| Thighs | 3,002 | 2,677 | —11 |
| Trunk | 5,003 | 4,158 | —17 |
| Legs | 1,876 | 2,144 | +14 |
| Feet | 1,042 | 1,055 | + 1 |
| Totals | 14,801 | 13,934 | — 5.8 |

# CLINICAL CALORIMETRY

SIXTH PAPER

## NOTES ON THE ABSORPTION OF FAT AND PROTEIN IN TYPHOID FEVER*

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In the course of other work on metabolism in typhoid fever it became advisable to analyze the feces of the patients. While these analyses constitute only a part of the problem in hand, the paucity of studies on the absorption of food in the febrile state appears to warrant publication of the results as a separate communication. For a complete discussion of the absorption of food in typhoid fever the reader is referred to the paper of Du Bois.[1]

Seven cases in all have been studied. The diets administered were modifications of the high calory diet employed in this clinic, that is, the proportions of fat and carbohydrate were varied to satisfy the requirements of the problem under investigation.

### METHODS OF CHEMICAL ANALYSIS

Urine and feces were collected in the manner described by Gephart and Du Bois.[2] The analysis consisted in the determination of fat and nitrogen in the feces and total nitrogen in the urine. Nitrogen was determined in all cases by the well known Kjeldahl method, fat in the feces was determined in part by the Kumagawa-Suto method, and later by a saponification procedure described by one of us.[3] Carbohydrate in the feces was not determined (see work of DuBois).

### CLINICAL DATA

All of the patients were admitted to Bellevue Hospital during 1913. As is customary on the service, each patient was given an enema every morning. Except when otherwise stated, the patients had from one to two formed or semiformed stools a day.

Emil C., aged 22 years, was admitted August 23, the fifth day of the disease. Widal reaction and blood culture positive. Illness, severe. The original fever lasted twenty-three days. After two days of normal temperature, the patient developed a severe relapse of twenty days' duration.

Thomas B., aged 60 years, admitted October 2, the fifteenth day of the disease. Widal reaction and blood culture positive. Illness, mild. Duration

* From the Russell Sage Institute of Pathology, in Affiliation with the Second Medical Division of Bellevue Hospital.

1. DuBois, E. F.: THE ARCHIVES INT. MED., 1912, x, 177.

2. Gephart, F. C., and DuBois, E. F.: The Organization of a Small Metabolism Ward, p. 829.

3. Gephart and Csonka: On the Estimation of Fat in Feces, Jour. Biol. Chem., 1914, xix, 521.

TABLE 1.—Daily Averages of Periods

| Patient and Weight | No. of Period | Stage of Typhoid Fever | Dates and Days of Disease, Inclusive | Range of Maximum Temp. F. | Food During Period, Averages per Day | | | Analysis of Feces, Average per Day | | Percentage Loss in Feces | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Carb., Gm. | Fat, Gm. | Nitrogen, Gm. | Fat, Gm. | Nitrogen, Gm. | Fat | Nitrogen |
| Emil C. ..... 60-62 Kg. | 1 | Early and late steep curve. | Sept. 11-16 (25-30) | 100.6-102.6 | 162 | 210 | 14.9 | 6.07 | 1.19 | 2.9 | 8.0 |
| | 2 | Late steep curve..... | Sept. 17-21 (31-35) | 99.8-101.0 | 483 | 74 | 15.0 | 6.30 | 2.89 | 8.5 | 19.3 |
| | | Relapse | | | | | | | | | |
| | 3 | Ascend. Temp. and early steep curve. | Sept. 22-Oct. 3 (36-47) | 100.0-104.8 | 331 | 127 | 13.6 | 2.53 | 1.24 | 2.0 | 9.1 |
| | 4 | Early and late steep curve. | Oct. 4-7 (48-50) | 102.0-104.0 | 174 | 225 | 15.0 | 7.85 | 2.31 | 3.5 | 15.4 |
| Thomas B. .. 74-76 Kg. | 1 | Contin. Temp. ..... | Oct. 7-10 (20-23) | 103.0-104.0 | 164 | 211 | 15.0 | 9.19 | 2.09 | 4.4 | 13.9 |
| | 2 | Early steep curve..... | Oct. 11-13 (24-26) | 102.4-103.0 | 479 | 71 | 14.9 | 5.80 | 1.89 | 8.2 | 12.6 |
| | 3 | Late steep curve..... | Oct. 14-16 (27-29) | 101.0-103.0 | 157 | 204 | 13.8 | 5.02 | 1.28 | 2.5 | 9.3 |
| Christian M. 80-82 Kg. | 1 | Late steep curve..... | Sept. 17-21 (24-28) | 100.8-101.8 | 483 | 74 | 15.0 | 7.04 | 2.38 | 9.5 | 15.9 |
| | 2 | First week conval. ..... | Sept. 22-25 (29-32) | 99.0- 99.6 | 160 | 210 | 15.1 | 6.85 | 1.62 | 3.3 | 10.7 |
| | 3 | First week conval. ..... | Sept. 26-28 (33-35) | 99.0- 99.4 | 431 | 165 | 16.6 | 7.00 | 1.97 | 4.6 | 11.9 |
| Ernest H. ... 91-92 Kg. | 1 | Early steep curve..... | Sept. 20-23 (18-21) | 101.2-103.0 | 160 | 212 | 15.4 | 7.08 | 1.83 | 3.3 | 11.9 |
| | 2 | Late steep curve..... | Sept. 24-27 (22-25) | 100.4-101.6 | 479 | 71 | 15.0 | 3.75 | 1.67 | 5.3 | 11.1 |
| | 3 | First week conval. ..... | Sept. 28-Oct. 1 (26-29) | 99.8-100.0 | 226 | 286 | 15.3 | 6.53 | 1.47 | 2.3 | 9.6 |
| Anton K. .... 50-52 Kg. | 1 | Contin. temp. and early steep curve. | Oct. 7-10 (16-19) | 103.8-104.6 | 47 | 173 | 15.0 | 6.61 | 1.37 | 2.4 | 9.1 |
| | 2 | Early and late steep curve | Oct. 11-16 (20-25) | 99.8-103.8 | 286 | 56 | 12.0 | 3.93 | 1.24 | 7.0 | 10.3 |
| Richard T. .. 36 Kg. | 1 | Early steep curve..... | Oct. 17-25 (18-26) | 101.0-104.2 | 285 | 57 | 14.3 | 1.63 | 0.84 | 2.9 | 5.8 |
| Morris S. .... 49.8 Kg. | 1 | Early steep curve..... | Oct. 30-Nov. 5 (20-26) | 102.2-104.0 | 309 | 143 | 15.6 | 9.74 | 2.60 | 6.8 | 14.8 |

of original fever, thirty-one days. After fourteen days of normal temperature the patient developed a relapse which lasted twenty days. The relapse was complicated by acute fibrinous pleurisy.

Christian M., aged 31 years, admitted September 8, the fifteenth day of the disease. Widal reaction and blood culture positive. Illness, mild. Duration of fever thirty days.

Ernest H., aged 30 years, admitted September 16, the fourteenth day of the disease. Blood culture and Widal reaction negative, though clinically the disease was undoubtedly typhoid fever. The illness was mild, the fever lasting twenty-four days.

Anton K., aged 18 years, admitted September 30, the ninth day of the disease. Blood culture positive. Illness, severe. Duration of fever twenty-five days. The patient suffered from diarrhea from the eleventh to the sixteenth day, passing three to nine stools a day. The first period of the analyses was not begun until the diarrhea had ceased.

Richard T., aged 14 years, admitted October 6, the seventh day of the disease. Widal and blood culture positive. Illness, severe. Duration of fever twenty-eight days. Mild cholecystitis developed on the twenty-fifth day. After one day of normal temperature a relapse occurred which lasted one week.

Morris S., aged 21 years, admitted October 17, the seventh day of the disease. Blood culture positive. Illness severe. Duration of fever thirty-four days. The patient suffered two relapses, the first severe, beginning on the thirty-sixth day and lasting twenty days; the second mild, beginning on the sixty-eighth day and continuing nine days.

TABLE 2.—Daily Averages and Percentage Loss

| Stage of Disease | No. of Periods | Av. Food Fat Gm. | Average Daily Loss | | Percentage Loss | |
|---|---|---|---|---|---|---|
| | | | Fat, Gm. | Nitrogen, Gm. | Fat | Nitrogen |
| Cont'd temperature ..... | 3 | 204 | 6.11 | 1.20 | 2.9 | 10.7 |
| Low fat, steep curve..... | 6 | 67 | 4.74 | 1.82 | 6.9 | 12.5 |
| High fat, steep curve..... | 5 | 199 | 7.15 | 1.84 | 3.8 | 11.9 |
| Convalescence ..... | 3 | 220 | 6.90 | 1.69 | 3.4 | 10.7 |
| Totals ..... | 17 | ... | 6.25 | 1.57 | 4.3 | 11.2 |

## DISCUSSION OF RESULTS

In Table 1 the results are expressed in terms of daily averages for the periods, which lasted from three to twelve days. The stage of the disease is designated by a description of the character of the temperature curve rather than by the actual day of the illness. As in previous papers, the stage of ascending temperature corresponds to the "first week," that of continued temperature to the "second week," that of the early steep-curve to the "third week," and that of the late steep-curve to the "fourth week." In the last two columns the losses are expressed in terms of percentage.

A summary of all the periods, in daily averages according to the stage of the disease, is given in Table 2.

ABSORPTION OF FAT

The total fat in the stools varied from 1.63 to 9.74 gm.

The mere statement of the amounts, however, conveys but little information; the stage of the disease and the quantity of fat in the food must be taken into consideration for a complete interpretation of the results. Likewise it should be stated that the expression of the results in percentage values is apt to be misleading unless one bears in mind that even the stools of fasting persons contain fat.

In the ascending and continuous temperature stages when the fat in the food varied from 127 to 273 gm. the total fat lost was from 2.53 to 9.19 gm. The percentage loss varied from 2.0 per cent. to 4.4 per cent.

The average total loss for this stage of the disease was 6.11 gm.; the average percentage loss was 2.9 per cent.

The results in the early and late steep-curve stages fall into two groups, according to the amount of fat which the patient received in his food.

Patients receiving from 56 to 74 gm. lost in the stools from 1.63 to 7.04 gm. of total fat, with an average loss of 4.4 gm. Attention should be directed to the unusually small loss of 1.63 gm. when the patient received 57 gm. The average percentage loss for this group was 6.9 per cent.

With patients receiving from 143 to 225 gm. of fat in the food, the total loss varied from 5.02 to 9.74 gm., with an average loss of 7.15 gm. In this group the relatively large loss of 9.74 gm. when the patient took only 143 gm. in the food should be noted. The average percentage loss for the group was 3.8 per cent.

In convalescence the total fat intake varied from 165 to 286 gm. The fat loss varied from 6.53 to 7.60 gm. The percentage loss was from 2.3 per cent. to 4.6 per cent.

If only those periods be considered in which the fat intake was relatively large, the percentage fat loss in the stools for all stages of the disease was 3.5 per cent. The loss in the febrile stage was 3.3 per cent., in convalescence it was 3.4 per cent. In other words, the patients in this series absorbed fat as well in the febrile stage of the disease as in convalescence.

The average fat loss for all the patients in all stages of the disease amounted to 4.3 per cent. This result is somewhat lower than that obtained by Du Bois, who found the average percentage loss to be 6.02 per cent. When the results are considered as a whole the conclusion appears to be warranted that fat is almost completely absorbed when given in very large quantity.

THE ABSORPTION OF PROTEIN

The quantity of protein in the diet was kept as nearly uniform as circumstances permitted. The lowest daily average intake of nitrogen was 12.0 gm., the highest was 16.6 gm.

The total nitrogen in the stools varied from 0.84 to 2.89 gm. The average total nitrogen for all stages of the disease amounted to 1.57 gm. The highest average loss, according to periods, of 1.84 gm. a day occurred in the steep-curve stage. The smallest average loss of 1.20 gm. occurred in the stage of continued fever. The quantity of fat in the food appeared to be without influence on the nitrogen loss.

The average percentage loss of nitrogen according to periods varied from 10.7 per cent. to 12.2 per cent. The average percentage loss for all stages of the disease was 11.2 per cent. This result is higher than that obtained by Du Bois, which amounted to 7.1 per cent. No explanation of this difference has been found.

SUMMARY

The feces of seven typhoid patients on the high calory diet have been analyzed for fat and protein in seventeen periods of three to twelve days each in length.

The average total fat loss for all the periods was 6.25 gm., corresponding to a percentage loss of 4.3 per cent. No differences were observed in the percentage absorption of fat in the early and later stages of the fever or up to the end of the first week of convalescence, when the intake was relatively large.

The average total nitrogen loss for all the periods amounted to 1.57 gm., corresponding to a percentage loss of 11.2 per cent.

The constant presence of fat and nitrogen in the feces, even in fasting, vitiates to some extent the validity of the results when expressed in percentages.

# CLINICAL CALORIMETRY

SEVENTH PAPER

## CALORIMETRIC OBSERVATIONS ON THE METABOLISM OF TYPHOID PATIENTS WITH AND WITHOUT FOOD*

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   F. Summary and conclusions.

### PREVIOUS INVESTIGATIONS

In a previous communication[1] the respiratory metabolism of typhoid patients as determined by means of the small Benedict respiration apparatus was discussed in detail. The literature of the subject was also reviewed, making repetition here unnecessary. Following this earlier work it was possible to continue the study of the typhoid patients by using the respiration calorimeter of the Russell Sage Institute of Pathology in Bellevue Hospital. In the immediately preceding papers of the series[2] the calorimeter and the metabolism ward have been described in detail and data have been given in regard to the normal controls and the absorption of food in typhoid fever. The patients studied were all in the metabolism ward and the calorimeter experiments were conducted in the manner described in the paper on normal controls. In our previous work on the general effect of the high calory diet on respiratory metabolism it was difficult to control the nourishment of the patients so as to determine the basal metabolism and the quantitative effects of different foods. It was, however, pos-

* Submitted for publication Feb. 10, 1915.

* From the Russell Sage Institute of Pathology in affiliation with the Second Medical Division of Bellevue Hospital, New York.

1. Coleman and DuBois: The Influence of the High Calory Diet on the Respiratory Exchanges in Typhoid Fever, THE ARCHIVES INT. MED., 1914, xiv, 168.

2. Clinical Calorimetry, Papers 1 to 6, this number. Brief preliminary reports were published in Jour. Am. Med. Assn., 1914, lxiii, 827, and ibid., 1914, lxiii, 932.

sible to demonstrate that the heat production of typhoid patients on a liberal diet was practically the same as that of fasting patients.

Patients with fever have been studied before in various calorimeters. Isaac Ott[3] of Philadelphia as early as 1892 made observations on a patient with malaria using a rather simple type of calorimeter which required a plus correction of 16 per cent. Likatscheff and Avroroff[4] in 1902 made classical experiments on a similar case. In 1909 Benedict and Carpenter[5] studied a few cases of mercurial poisoning with fever in the Middletown calorimeter. An excellent summary of the literature is given in the Russian publication.[4] It is sufficient to say that the rise and fall of body temperature have been ascribed at various times to every possible combination of increase and decrease in heat production and heat elimination. The Russians used the Paschutin calorimeter in which the patient was kept for twenty-two hours, feeding herself and apparently moving about the chamber during the day whenever she felt inclined to do so. The heat elimination was measured in periods of two hours each and the body temperature was determined every two hours, apparently by means of a mercurial thermometer in the axilla. The $CO_2$ and water elimination were measured in two-hour periods but the oxygen consumption and consequently the respiratory quotient could only be determined by the change in body weight during twenty-two hours. This method seems to have given satisfactory results, since the quotients correspond to those usually found under similar conditions and calculation of the indirect calorimetry in the three experiments gives results which come within —6 per cent. +6 per cent. and +12 per cent. of the direct calorimetry. The Russians themselves calculated the total heat production by adding the calories stored in or lost from the body as the temperature rose and fell to the calories eliminated by means of radiation, conduction and vaporization. They came to the conclusion that the rise of body temperature was due to an increase in heat production. Benedict and Carpenter studied their fever patients under similar conditions, but determined the oxygen, $CO_2$ and the heat elimination in periods from two to six hours in length. If one takes the periods when their subjects

3. Ott, Isaac: The Modern Antipyretics, Ed. 2, Easton, Pa., 1892; Fever, Its Thermotaxis and Metabolism, New York, 1914.

4. Likatscheff and Avroroff: Investigations of Gaseous and Heat Exchange in Fevers. Reports of the Imperial Military Academy, St. Petersburg, 1902, v, parts 3 and 4. We are indebted to Dr. F. G. Benedict of the Carnegie Nutrition Laboratory for permission to consult his translation of this important work. Excellent abstracts in English have been published in a paper by A. I. Ringer (Physiology and Pathology of Fever, Am. Jour. Med. Sc., 1911, cxlii, 485) and in the monograph on Fever by Ott.

5. Benedict and Carpenter: Preliminary Observations on Metabolism During Fever, Am. Jour. Physiol., 1909, xxiv, 203.

had a body temperature of 38 C. or over and calculates the indirect calorimetry, using the oxygen and quotients, it is easy to determine the divergence of the direct from the indirect calorimetry. The percentage differences are as follows: +5. +10. —9 +9. +2.

## METHODS USED

The present work with the calorimeter was undertaken to extend the previous observations and clear up some doubtful points which could be settled only by a most careful control of the diet and by a comparison of the direct and indirect calorimetry. The fact that it was impossible to bring typhoid patients into nitrogen equilibrium unless the diet greatly exceeded the heat production as calculated from the oxygen consumption, suggested the possibility that the method of calculating the indirect calorimetry might be incorrect. There remained also the old work on fever in which abnormally low respiratory quotients were obtained, leading several investigators to believe that the metabolism in fever was radically different from that in health. Finally, it was hoped that it would be possible to determine whether the rising body temperature was due to an increasing heat production or to a decreasing heat elimination.

The subjects studied were typhoid patients who entered Bellevue Hospital in 1913 and 1914. There was some selection of cases in an effort to obtain men in the early stages of the disease who were intelligent enough to cooperate. Most of the patients were taken to the metabolism ward so early in the disease that it was impossible to predict whether the fever would run a mild or severe course. Several patients were transferred from the First Medical Division through the kindness of Dr. Norrie and Dr. Miller to whom we are much indebted.

All of the patients were put on the high calory diet described in previous publications[6] and trained to take the large amounts of food. The very large amounts formerly given to some patients were not administered and the calories seldom exceeded 3,000 a day. An attempt was made to keep the food nitrogen at 15 grams. The stools exceeded two a day only on the occasions mentioned in the histories, and there was seldom abdominal distention. None of the patients was tubbed, although cold sponges were occasionally given to make the patient

6. Shaffer and Coleman: Protein Metabolism in Typhoid Fever, THE ARCHIVES INT. MED., 1909, iv, 538-600; Coleman: Diet in Typhoid Fever, Jour. Am. Med. Assn., 1909, liii, 1145; The High Calory Diet in Typhoid Fever — A Study of One Hundred and Eleven Cases, Am. Jour. Med. Sc., 1912, cxliv, 659; DuBois: The Absorption of Food in Typhoid Fever, THE ARCHIVES INT. MED., 1912, x, 177; Coleman: Weight Curves in Typhoid Fever, Am. Jour. Med. Sc., 1912, exliv, 659; Diet and Metabolism in Fever, Trans. Fifteenth Internat. Cong. on Hyg. and Demog., 1912.

feel more comfortable when the temperature reached 104. Nervous symptoms were not prominent in any case, although one or two of them were mildly delirious for a few days. Most of the patients were cheerful throughout their illness and read the daily papers. It is estimated that their activity increased their metabolism about 10 per cent. above the basal level, although this figure is necessarily only an approximation.

### CASE REPORTS

CASE 1.—Morris S. (severe typhoid) tailor, English Hebrew of Russian extraction, 21 years old, admitted October 17, discharged January 30.

*History.*—Previous history unimportant; patient is not alcoholic. He landed from England Sept. 28, 1913. October 10 he began to suffer from pain in his abdomen, chest and back. On the thirteenth he had a nose bleed. Since the onset of symptoms he has had no appetite and has been constipated.

*Physical Examination.*—Patient is a well-nourished young man of small frame and short stature, being 164 cm. tall. There is slight cyanosis of lips and ears, the tongue is heavily coated, tonsils hypertrophied and congested. There is an occasional subcrepitant râle at the apex of the left lung. The spleen is palpable.

Blood taken October 18 gave a negative Widal test but developed a growth of typhoid bacilli. The spleen edge was felt 4 cm. below the costal margin and a few rose spots were present. October 24 the Widal was positive. The next day there were a few sibilant and sonorous sounds over the chest, clearing up by the twenty-seventh. The patient had been on a diet with high carbohydrate and low fat, and on October 23 and 24 had shown abdominal distention with about four liquid stools a day. The distention and diarrhea ceased when the fat was increased and the very large amounts of carbohydrate stopped. For the next month he had only one or two movements a day. October 30 he became a little irrational and his color was grayish, his pulse soft and very dicrotic. November 3 he was irrational in the calorimeter and wrote several notes about the animals which he saw in his hallucinations. The next day he was in much better condition, the pulse was stronger and his physical condition improved steadily.

November 16 the temperature began to rise after it had been practically normal for five days. He felt perfectly well and was bright and cheerful, in spite of a temperature of 104, until the evening of the eighteenth when he had a sharp pain in the right side of the abdomen. This disappeared the next day. This relapse was almost as severe as the original infection, but the patient was not quite so toxic and was never irrational. The temperature remained normal from December 7 to 17. From November 23 to 26 he had frothy stools but these became formed once more when the fat in the diet was increased.

December 17 a second relapse began and lasted until the 27th. During the period of rising temperature he was somewhat apathetic and suffered from headache and was fretful during the two days of high fever. His general condition remained excellent and he never realized that he was having a relapse. Following this, convalescence was rapid, since he had lost practically no weight during his illness. During the next year he reported at the hospital several times, always in excellent condition and five or ten pounds heavier than ever before in his life.

In December, 1914, he returned to the metabolism ward for two days, giving us the opportunity to determine his basal metabolism and the specific dynamic action of the protein meal.

This history is given in detail since Morris S. was placed in the calorimeter twenty-four times. He was an exceptional patient, in that he ate the prescribed diet practically every day and enjoyed the distinction of going in the calorimeter more often than his fellow patients. Nothing made him happier than the extra attention he received on calorimeter days, and as a result he did exactly what he was told to do. We were particularly fortunate in being able to determine the specific dynamic action of protein and the basal metabolism while he was in perfect health, a year after his infection.

CASE 2.—Charles F. (severe typhoid), elevator constructor, born in New York, 24 years old, admitted November 4, discharged January 12.

*History.*—Lives in same house as his nephew Howard F., who has similar symptoms. On October 28 he began to suffer from anorexia, malaise and headache. On November 3 he had a nose bleed. He did not take to bed until admitted to the hospital.

*Physical Examination.*—Fairly well-nourished young man of medium frame, 166 cm. tall. He is moderately prostrated; there are several rose spots and the spleen edge is palpable 4 cm. below the costal margin.

Blood taken the day after admission gave a positive Widal test and showed a growth of typhoid bacilli. November 7 and again on the eighth he had a small intestinal hemorrhage of about 200 c.c. His general condition remained fair; he was rational and the toxemia not marked. He was given a daily sponge for his high temperature. At this time he took his food very badly and after the hemorrhages ceased it was impossible to give even 2,000 calories. November 14 to 17 he had a severe follicular tonsillitis and his toxemia was marked. Rose spots appeared in crops. On the nineteenth he had a hemorrhage of about 250 c.c. and was very toxic and apathetic for the next week. His pulse was very soft, systolic blood pressure being 95 mm. mercury. By December 3 the temperature was normal, he was much improved and was reading the paper every day. Convalescence was rapid. Throughout the disease he had one formed stool each day.

This patient was very intelligent and was anxious to help us in every way possible but his digestion made it difficult for him to take the food. He was very quiet while in the calorimeter.

CASE 3.—Howard F. (typhoid fever of moderate severity), schoolboy, born in New York, 12 years old, admitted November 4; discharged January 22.

*History.*—Lives in the same house as his uncle, Charles F. He was perfectly well until October 26 when he had a severe headache. On the twenty-eighth he felt so sick that he took to bed. The next day he had a chill; vomited. He had nose bleed on the thirty-first and on the day of admission.

*Physical Examination.*—Patient is a tall, slender boy who has not yet reached the age of puberty; height 160 cm.; the cheeks are flushed and he looks acutely ill. Heart apex in the fourth space 8.5 cm. to the left of the midline. There are several rose spots on the abdomen; the spleen is not palpable.

On November 14 the blood culture showed typhoid bacilli. November 12 showers of subcrepitant râles appeared at the left base and the next day sibilant and sonorous sounds were heard all over the chest. His general condition was good, and although he was very apathetic, he was perfectly rational. He took his food very poorly, vomiting often. By the seventeenth he was very thin, quite toxic, very drowsy but rational. The pulse was soft but of fair quality.

The sibilant and sonorous sounds persisted until the twenty-fourth, by which time the temperature was falling, the appetite much better and the patient able to read the paper. Convalescence progressed rather slowly. On December 10 he passed two ascarides. The heart action was rapid on exertion and on the eighteenth the apex was in the fourth space 9.5 cm. from the midline. He left the hospital in good condition. Throughout his illness he had one stool a day.

The boy was very intelligent and made a good subject for the calorimeter.

CASE 4.—Karl S. (typhoid fever of moderate severity), stoker on steamer to South America, German, 24 years old, admitted December 29; discharged Feb. 18.

*History.*—Returning on a voyage from Brazil he landed at San Domingo for a few days, reaching New York December 20. Two days later he began to suffer from headache, weakness, lassitude, anorexia and nausea. On the twenty-fourth he began to have daily chills.

*Physical Examination.*—One hundred and sixty-eight cm. tall, muscular and well nourished. His face is flushed and he looks stuporous. No spots, spleen not palpable. Blood taken the day after admission gave a negative Widal but positive growth of typhoid bacilli. January 1 rose spots appeared and the spleen became palpable. On the third he was prostrated, apathetic and showed slight subsultus tendinum. The pulse was soft and dicrotic and the abdomen distended. When carbohydrates were pushed too high he became distended, but this trouble disappeared when the amounts were decreased. By January 7 he was anxious about his condition and easily frightened. On the tenth his condition was satisfactory and by the twenty-sixth he was afebrile and was reading and studying every day. He was very hungry during his rapid convalescence. February 14 he developed tonsillitis. The temperature rose to 101 and the pulse became rapid. He did not feel sick and resented being confined to bed. On the seventeenth he became insubordinate and was discharged from the hospital. Two weeks later he returned on a visit in good condition.

This patient was a rough sailor of sullen disposition and made a rather restless subject for the calorimeter. During most of the observations on this man one of the water thermometers was being repaired and the method of direct calorimetry could not be used.

CASE 5.—Thomas B. (typhoid fever, mild; followed by acute fibrinous pleurisy). Laborer, Irish, 60 years old, admitted October 2, discharged December 8.

*History.*—Moderately alcoholic. About September 18 began to suffer from malaise, anorexia and fever.

*Physical Examination.*—Large well-nourished man, who looks acutely ill. He is apathetic and slightly cyanotic.

Blood taken the day of admission gave a positive Widal and showed a growth of typhoid bacilli. Many rose spots appeared but the spleen was never palpable. He took his food well and was never very ill. From October 22 to November 6 the temperature was normal. Then it rose gradually to 104 and fell slowly reaching normal on the twenty-sixth. During this time he developed dulness, bronchial voice and breathing at the left base, the signs being attributed to a pleurisy rather than pneumonia. He made a rapid convalescence.

CASE 6.—Richard T. (mild typhoid). Mulatto boy, born in New York, 14 years old, admitted October 6, discharged November 24.

*History.*—About September 30 began to suffer from headache, weakness, constipation and occasional abdominal pains.

*Physical Examination.*—Well nourished active boy who has not yet reached puberty. There are a few rose spots and the spleen is palpable.

The day after admission the blood culture gave a positive Widal and showed a growth of typhoid bacilli. The disease ran a mild and uneventful course, in spite of high evening temperatures, until October 25, when he developed slight pain and tenderness over the gall bladder, lasting two days. The temperature reached normal October 29, but rose again in a mild relapse lasting till November 6. Convalescence was rapid.

The boy was somewhat mischievous and was very active throughout his stay in the hospital. While in the calorimeter he spent most of his time looking out of the window and was not as quiet as most of the patients.

CASE 7.—Anton K. (mild typhoid), factory worker, Austrian, 18 years old, admitted September 30, discharged November 18.

*History.*—September 22 he began to have daily chills and fever, lost his appetite, felt exhausted and had severe pains in the epigastrium.

*Physical Examination.*—This showed a well-nourished man, apathetic and acutely ill. Typhoid bacilli were found in the blood. At the height of his fever he was prostrated and developed slight subsultus tendinum. He took his food well and was in good condition on October 16, the first day of normal temperature.

CASE 8.—Rose G. (severe typhoid), born in New York, 12 years old; admitted September 19, discharged November 26.

*History.*—Menstruation has not yet begun. The girl is tall and very thin and is somewhat deficient mentally. She went through a severe course of typhoid, with marked emaciation. Blood culture showed typhoid bacilli. During the disease she had râles at both bases and developed bed sores because she had all her life been incontinent of urine. Temperature reached normal October 29, and she was up and about on November 17. During convalescence she ate enormous amounts of food, with very slight gain in weight. She was not in the metabolism ward and exact figures for the food were not obtainable, but it seemed as if the discrepancy between food and gain in weight could be accounted for only by a greatly increased metabolism. The first hour she was in the calorimeter she was quiet, but during the second hour she voided in bed and began to cry, making it necessary to end the observation.

CASE 9.—Edward B. (severe typhoid), longshoreman, born in Ireland, 36 years old; admitted October 3, 1914, discharged February, 1915.

*History.*—He remembers no previous illnesses. October 1 he began to suffer from headache, pains all over the body and abdominal cramps, with diarrhea and three to four stools a day. He had no nausea and the appetite was good.

*Physical Examination.*—Well-nourished man of medium frame, fairly muscular. He is dull and apathetic and moderately prostrated. The heart is rapid, not enlarged, the lungs are clear, abdomen soft, spleen palpable. There are a few rose spots.

The blood on October 4 was sterile, but gave a positive Widal test. On the sixth he was very drowsy; by the tenth he was comfortable and eating well. October 13 the temperature had again risen, the pulse rate had jumped to 120 and the quality of the pulse was poor. On the twentieth he was much better and was taking his food well, but the abdomen was slightly distended. By November 1 the temperature was almost normal and the general condition excellent in spite of a small rapid weak pulse. By November 7 the temperature was up again, and he was beginning to feel indisposed. The appetite was poor and the pulse rate between 138 and 148. During the next few days the pulse was very rapid, slightly irregular, and very weak. He was very toxic but was rational except for short periods when the mind was a little hazy. November 16 he had a small hemorrhage with a short period of collapse, but recovered quickly. His condition improved steadily until December 3 when the temper-

ature rose once more and he suffered from a moderately severe relapse, lasting until December 21. Following this was a period of three days of normal temperature and then a fourth relapse, very mild in character lasting only three days. During the whole period of his illness his nutrition remained good; he was always cheerful and read the newspaper almost every day.

CASE 10.—John K. (typhoid fever, mild), deck hand, Polish, aged 35; admitted Dec. 12, 1914, discharged Jan. 27, 1915.

*History.*—December 2, began to suffer from malaise. December 5 had a severe chill and took to bed; since then has had chills almost every day. Has had continuous headache, has vomited frequently and has been constipated.

*Physical Examination.*—Tall and thin, fairly muscular. Tongue dry, coated, fissured. Heart and lungs clear, spleen palpable, many rose spots.

December 12, the blood culture was sterile but the Widal positive. On the thirteenth he had his last chill, on the sixteenth he was apathetic and prostrated, pulse was slow and dicrotic, there was a patch of herpes on the upper lip. As the temperature fell during the next few days his condition improved rapidly, but the apathy remained until the temperature was normal, and he was unusually quiet, remaining almost motionless all day long. Convalescence was rapid.

## DISCUSSION OF RESULTS

*Law of Conservation of Energy in Fever.*—The law of conservation of energy has been shown to apply to the lower animals, to normal men and to babies, and has been discussed in the previous paper (Paper 6) on normal controls, in which it was demonstrated that with normal men a satisfactory agreement between the direct and indirect calorimetry could be obtained in periods as short as one hour. While there are few who doubt that the law applies to men with fever, it may not be superfluous to bring forward proof.

An agreement of the direct and indirect calorimetry within the limits of experimental error indicates that protein, fat and carbohydrate are oxidized to the same or approximately the same end products as in health and that in the oxidation they give off the standard amounts of heat. The method of calculating the indirect calorimetry depends on the assumption that the calories furnished by each gram of protein, fat and carbohydrate correspond to the standard figures of Loewy,[7] protein 4.32, fat 9.46, starch 4.18. The results obtained by the method of direct calorimetry, which is dependent only on fundamental laws of physics, must remain the standard method of comparison when considering large groups of experiments. Once the agreement has been proved for the group, the method of indirect calorimetry is preferable for individual experiments as has been shown in previous papers on account of the technical difficulty of the method of direct calorimetry in short periods.

Table 1 gives a summary of the percentage divergence of the direct and indirect calorimetry in all the experiments on the typhoid patients,

7. Loewy: Der respiratorische und der Gesamtumsatz, Oppenheimer's Handb. der Biochem, 1911, iv, 280.

the great majority of them being three hours long. In all cases the indirect method was used as a standard. If we consider the total measurement of 12,822 calories, we find the direct method, as calculated from the rectal temperature, gives results only 2.2 per cent. lower than the indirect. In almost half of the experiments the body temperature was measured by a thermometer of two units strapped on the thorax in the region of the apex of the heart and just below the right nipple, each unit being covered by a pad of cotton about 15 cm. square and 4 cm. thick. The rectal thermometer was inserted about 12 cm. beyond the sphincter. In a previous paper attention has been called to the fact that in these typhoid cases in which both methods were tried

TABLE 1.—PERCENTAGE DIVERGENCE OF DIRECT FROM INDIRECT CALORIMETRY IN THE INDIVIDUAL EXPERIMENTS

| Percentage Divergence | Number of Experiments Falling in Each Group | | | | | |
|---|---|---|---|---|---|---|
| | According to Rectal Temperature | | | According to Surface Temperature | | |
| | + Divergence | − Divergence | Total | + | − | Total |
| 0- 5..... | 17 | 22 | 39 | 11 | 7 | 18 |
| 6-10..... | 3 | 15 | 18 | 2 | 7 | 9 |
| 11-17..... ..... | 1 | 3 | 4 | 0 | 1 | 1 |
| Total..... | .. | .. | 61 | .. | .. | 28 |
| Average Error.. | .. | .. | ±4.9% | .. | .. | ±4.0% |

| | Indirect | Direct* | Divergence |
|---|---|---|---|
| | | | % |
| Total calories measured in all experiments..... | 12,822.03 | 12,539.67 | −2.2 |
| Excluding first periods..... ..... | 8,470.93 | 8,488.97 | +0.2 |
| Calories measured in febrile experiments excluding all first periods ..... | 5,720.21 | 5,583.55 | −2.4 |

* According to rectal temperature.

slightly better results were obtained by using the surface thermometers to give the temperature changes of the body than by using the rectal. In the long run the rectal thermometer is the more reliable, since it is not so easily displaced by bodily movement, but enough evidence has been accumulated to show that the rectal temperature does not always change in the same degree and not always in the same direction as the average body change. As the body cools off there may be a relative increase in the heat near the surface of the body, since this is the place that most of the heat is dissipated. The opposite takes place when the temperature is rising. On account of the rapid circulation of blood

there is, of course, a tendency for the temperature curves of the different parts of the body to follow the deep temperature as measured in the rectum.

In the sixty-one experiments in which the rectal temperature was measured the average divergence of the indirect calorimetry from the direct calorimetry (as based on the rectal temperature) is only ±4.9 per cent. In twenty-eight of these experiments it was possible to base the calculations on the changes in the surface temperature, with an average divergence of 4.0 per cent. using this latter method. This divergence of 4 or 5 per cent. is not more than one often finds among normal controls, since the technic is difficult even with trained subjects. The reason for the total minus error of 2.2 per cent. is not clear. The largest part of this error frequently falls in the first hour, especially in patients with fever, and we have been led to suspect that the subject continues to give out heat to the wooden bed frame and to the bedding even after he has been on the bed for an hour. If we excluded from our calculations the first periods, while the calorimeter is still coming into thermal equilibrium, we find that the direct and indirect methods agree within 0.2 per cent. If we consider only those experiments made during the febrile period, we find a larger proportion show a minus error in the direct calorimetry than when we take all the experiments put together. Excluding the first hours of each experiment, however, the direct calorimetry gives a total only 2.4 per cent. lower than the indirect. The difference is so small that it might be found in a group of normal controls. It may be entirely accounted for by the difficulty in measuring the average body temperature during fever.

*Basal Metabolism in Typhoid Fever.*—In Paper 4 of this series the reasons have been given for the selection of the standard of the average normal basal metabolism. The figure of 34.7 calories per square meter per hour as based on Meeh's formula has been used in all the calculations. It was impossible to use the new surface formula as a standard since this was not devised until most of the typhoid work had been completed.

The relationship of the basal metabolism of the typhoid patients in the various stages of the disease to the normal is shown in Table 2. This corresponds in a striking manner with the averages of the fasting typhoid patients investigated by Kraus, Svenson, Grafe and Rolly and collected by us in a previous publication.[1] It is evident from the general trend of the results that the total metabolism increases and falls in a curve roughly parallel with the body temperature, and that the period when it drops below normal in many patients corresponds with the period of subnormal temperature which occurs so often in the first week of convalescence. From a study of the results obtained by the

calorimeter and by various smaller types of respiration apparatus, it is apparent that there is considerable variation in the heat production of different patients and the same patient at different stages of the fever. While we can state that the average increase in typhoid fever is approximately 40 per cent., we must remember that figures over 50 per cent. are frequently encountered. This should make us cautious in drawing too many deductions from feeding experiments unaccompanied by determinations of the respiratory metabolism. It should also be remembered that typhoid fever is the only fever which has been thoroughly investigated and that if variations occur in this one disease the variations may be quite different in other febrile diseases such as erysipelas, pneumonia, puerperal fever, etc.

TABLE 2.—Basal Metabolism, According to Periods of Typhoid Fever

| Periods | Number of Patients | Number of Observations | Average Per Cent. Rise Above Average Normal 34.7 Cal. per Sq. M. | Average Respiratory Quotient |
|---|---|---|---|---|
| Ascending temperature | 2 | 2 | +37 | 0.79 |
| Continued temperature | 5 | 7 | +42 | 0.77 |
| Early steep curve | 3 | 4 | +26 | 0.82 |
| Late steep curve | 3 | 3 | +16 | 0.82 |
| Relapse— | | | | |
| Ascending temperature | 2 | 3 | +25 | 0.82 |
| Continued temperature | 2 | 2 | +51 | 0.76 |
| Early steep curve | 2 | 4 | +36 | 0.78 |
| Late steep curve | 1 | 1 | +16 | 0.79 |
| Convalescence— | | | | |
| First week | 3 | 4 | — 2 | 0.91 |
| Second week | 3 | 5 | + 6 | 0.88 |
| Third week | 1 | 1 | +17 | 0.81 |
| Fourth week | 2 | 2 | +15 | 0.86 |
| Fifth week | 2 | 2 | + 4 | 0.81 |

Benedict and his co-workers in all their recent publications have drawn attention to the fact that pulse rate and total metabolism show curves which are roughly parallel. As might be expected this parallelism is not as apparent in typhoid fever as in the conditions they have studied. Typhoid is characterized by a slow pulse in the first two weeks when the metabolism is high. The experiments here reported do not show any striking agreement in the rise and fall of the two curves.

*The Specific Dynamic Action of Food.*—When studying the effects of the high calory diet in typhoid fever with the small Benedict respira-

tion apparatus, the writers noted the fact that the metabolism of liberally fed typhoid patients was scarcely raised above the metabolism of fasting typhoid patients. The conclusion was drawn that food exhibits little or no specific dynamic action in typhoid fever. One of the chief objects of the present research was to study this striking phenomenon more closely, inasmuch as some observers, among them Von Noorden,[8] have stated that the specific dynamic action of food was increased in fever, exophthalmic goiter and several other conditions.

We have seldom kept typhoid patients in the calorimeter for periods exceeding three or four hours. After this length of time the patients often become restless and bored, making the results unreliable. This

TABLE 3.—SPECIFIC DYNAMIC ACTION OF PROTEIN AND CARBOHYDRATE IN HEALTH, FEVER AND CONVALESCENCE

| Subjects | Number of Experiments | Average Gm. of Nitrogen or Glucose in Food | Average Gm. Food per Kg. Body Weight Nitrogen or Glucose | Average Per Cent. Rise in Metabolism |
|---|---|---|---|---|
| Protein meal | | | | |
| Two normal men* | 2 | 10.1 | 0.147 | 9.3 |
| Four febrile patients | 6 | 8.6 | 0.174 | 4.5 |
| Four convalescents | 5 | 10.2 | 0.217 | 16.6 |
| Commercial glucose | | | | |
| Three normal men* | 3 | 115.0 | 1.6 | 9.1 |
| Two febrile patients | 4 | 115.0 | 2.2 | 1.0 |
| Three convalescents | 3 | 115.0 | 2.7 | 9.8 |

* Since the completion of Paper 4 two more normal controls have been given the test meals. Morris S. on Dec. 18, 1914, showed a rise of 6.5 per cent. after a meal containing 9.6 gm. N.; Albert G. on Jan. 6, 1915, showed an increase of 9.0 per cent. in his metabolism after 115 gm. commercial glucose.

has made it impossible to determine the basal metabolism in a two hour experiment and follow it immediately by a three or four hour experiment to find out the effect of food. Moreover, in such a long period the temperature might change several degrees, making the results difficult of interpretation. In the case of normal controls, the basal metabolism is so uniform from day to day that very accurate results can be obtained by determining the basal metabolism and the metabolism after food on different days. In fever the change in the level of metabolism from day to day makes the results less accurate but the error will be small if certain precautions are taken. The level of basal heat production changes in a fairly gradual and uniform curve and

8. Von Noorden: New Aspects of Diabetes, New York, E. B. Treat & Co., 1912, p. 20.

there is but a small change in twenty-four hours unless the temperature or the general condition of the patient changes markedly. For this reason the effect of a given meal has been determined sometimes the day before, sometimes the day after and sometimes the day between basal experiments. The protein meal was given six times in the febrile period and the glucose meal four times. It is against the laws of probability that the basal metabolism should take a sudden change in the same direction on all these days.

The fact that the average amount of protein given in the febrile period was less than that given in health was due to the poor appetite of the patients at the height of the disease. Even in health and in

TABLE 4.—CHART SHOWING NEGATIVE NITROGEN BALANCES IN TYPHOID PATIENTS WHO RECEIVE FOOD CALORIES IN EXCESS OF CALCULATED HEAT PRODUCTION

| Patient | Dates or Days of Disease Inclusive | Days in Period | Range of Maximum Temperature, Degrees F. | Calculated Heat Production, Cal.* | Food Calories* | Food N, Gm.* | Nitrogen Balance Gm.* |
|---|---|---|---|---|---|---|---|
| Morris S. | Oct. 23-Nov. 2 | 12 | 102.8-104.6 | 2,206 | 2,863 | 16.4 | —4.4 |
| | Dec. 19-24 | 6 | 101.9-105.1 | 2,085 | 2,989 | 13.2 | —2.4 |
| Charles F. | Nov. 28-30 | 3 | 101.2-103.4 | 1,752 | 2,458 | 12.0 | —4.6 |
| Karl S. ... | Jan. 12-18 | 7 | 101.0-105.0 | 2,197 | 2,985 | 16.1 | —3.2 |
| | Jan. 19-22 | 4 | 98.8- 99.0 | 1,678 | 2,819 | 14.6 | —1.9 |
| John K.... | Jan. 15-20 | 6 | 103.2-104.0 | 2,568 | | | |
| Frank W.† | Days of Disease 11-14 | 4 | 104.0-105.4 | 2,200 | 2,250 | 11.3 | —5.0 |
| | 15-19 | 5 | 103.0-104.0 | 2,228 | 3,330 | 15.3 | —3.3 |
| | 20-23 | 4 | 101.0-103.6 | 2,054 | 2,362 | 15.9 | —1.5 |

* Figures given are averages for twenty-four hours.
† Taken from Coleman and Du Bois.[1]

convalescence the meal is a large one, containing almost as much protein as most people consume in a day. We must remember also that the normal controls weighed 75 and 63 kg. when they took this meal and that the typhoid patients weighed 51, 58, 35, and 54 kg., respectively. As is shown in Table 3 the controls received less nitrogen per unit of body weight than the fever patients. We can therefore state that protein and glucose exhibit a much smaller specific dynamic action in typhoid fever than in health, while in convalescence from the disease the specific dynamic action seems to be greater than normal. In the case of glucose there was practically no specific dynamic action in fever, and in the case of Morris S. the specific dynamic action of the protein was very slight.

The cause for this phenomenon has not yet been definitely ascertained but the most plausible theory was stated by Dr. Graham Lusk[9] in the discussion on the symposium on nutrition at Atlantic City in 1914. He called attention to the well known fact that if the metabolism be increased by lowering the environmental temperature there may be

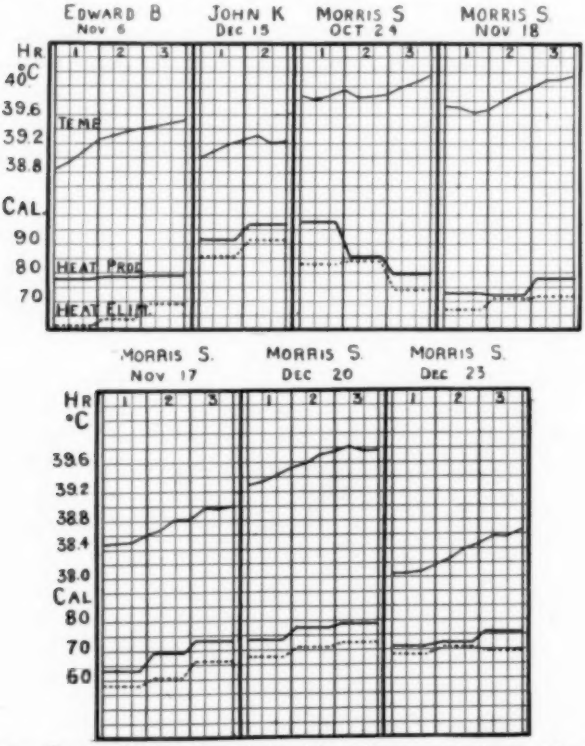


Chart 1.—Curves showing the relationship of heat production and heat elimination in fever. Rising temperature. The uppermost line shows the rectal temperature as measured every twenty minutes. The heavy continued line represents the heat production in hourly periods as determined by the method of indirect calorimetry. The dotted line gives the heat elimination as determined by the measurement of the calories of radiation, conduction and vaporization. The difference between the levels of these two lines represents the heat stored in the body as the temperature rises. Note the fact that in every case except one the heat elimination increases with a rising temperature.

no specific dynamic action as usually induced by ingested food. In like manner if the metabolism be raised in fever, food ingestion may cause no increase. He also stated that since protein metabolism in fever

9. Lusk: Jour. Am. Med. Assn., 1914, lxiii, 831, foot of page.

can never be reduced to as low a level as is present in the normal organism, therefore protein ingestion in fever often merely serves to replace the protein already breaking up in increased quantity, and such protein ingestion would not then serve to increase the heat production.

*The Regulation of Body Temperature.*—The study of the regulation of body temperature is one that demands the utmost accuracy of technic. The question at issue is whether a rise in temperature is due to an increase in heat production or a decrease in heat elimination. Previous investigators have tried to solve this problem on data obtained from the direct calorimetry alone, or from the indirect calorimetry accompanied by measurements of body temperature. In either of these two methods the whole calculation would depend on the exact

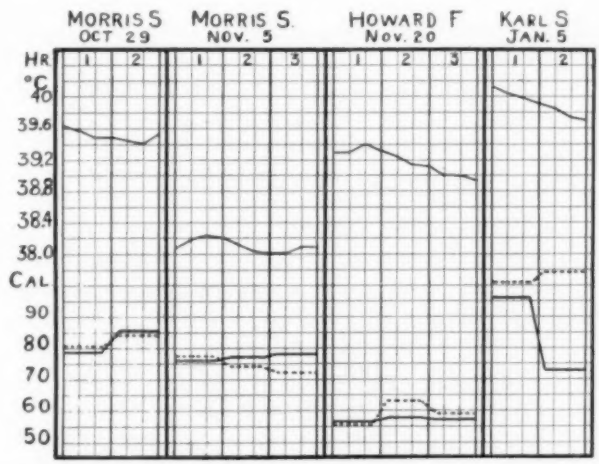


Chart 2.—Curves showing the relationship of heat production and heat elimination in fever. (See legend Chart 1.) Temperature level or falling. In the last two experiments it will be noted that the heat elimination rises above the production.

measurement of the average change in body temperature, the exact calculation of specific heat of the body and the amount of heat stored in or lost from the body. It has been shown in this and preceding papers that these measurements and calculations are the weakest points in the science of calorimetry and it is only very recently that the technic has been so developed that investigators have attempted a comparison of the methods of direct and indirect calorimetry in periods shorter than six to twelve hours, periods obviously too long for the study of the problem in question. If, in a period of experimentation, the results obtained by the method of indirect calorimetry and by the method of

direct calorimetry, using either the rectal or the surface temperature, do not agree within 5 per cent., we must suspect some error, probably in the measurement of the average body temperature change. For this reason we have eliminated from the discussion all experiments in which the two methods do not agree within 5 per cent. It is also preferable to eliminate all experiments after the taking of food and all experiments in which the subject was not quiet. This gives us eleven experiments during the febrile period in which the technic left nothing to be desired.

In Chart 1 are grouped those experiments in which there was a rising body temperature. The dotted line shows the total heat eliminated from the body by means of radiation, conduction and vaporization. The continued line shows the heat production as determined by the method of indirect calorimetry, which does not use a single factor that affects the dotted line. With a rising body temperature the heat production within the body must be greater than the elimination to provide for the storage of heat in the tissues. Many are of the opinion that the rise in temperature is chiefly due to a decrease in the heat elimination. This we find to be the case only in the last hour of one of the seven observations, there being a sharp drop in both heat production and elimination towards the end of the experiment on Morris S. on October 24. In all the other periods the rising temperature was accompanied by an increasing heat production which outweighed the increasing heat elimination.

In Chart 2 which shows periods in which the body temperatures were fairly level the production and elimination were about equal and constant. In the two observations with falling temperature the heat production remained fairly level while the elimination was increased.

*Heat Production, Weight and Nitrogen Equilibrium.*—In the cases here studied it is possible to make a comparison of the caloric intake and the caloric output. The intake consists of the calories of the food. The output is made up of many factors, but principally of calories lost by radiation, conduction and the evaporation of water. The first and most important consideration is the determination of the basal heat production as measured by the methods of direct and indirect calorimetry. As has been shown above, the two methods agree within 2 per cent. The actual heat production during the different hours of the day can depart from the basal as a result of various factors. We have shown above that the ingestion of large amounts of food causes but a slight increase in metabolism, averaging less than 5 per cent. in the case of protein and only 1 per cent. in the case of carbohydrate. These increases may be considered the maxima since the amounts of foods given were the largest the patient could take and the hours of the

observation were the hours of the greatest specific dynamic action. The exact percentage rise caused by the stimulation of the food taken during the whole day is problematical but may be estimated as about 3 per cent. The percentage of calories lost in the feces has been studied in two previous papers and has been found to be practically normal. The calories lost as urea and in the feces are taken into consideration in the calculation of the fuel values of the food. In the one case in which there was alimentary glycosuria (Frank W.),[1] the calories lost as dextrose have been subtracted from the intake. In a previous paper the writers have discussed the evidence against an abnormal loss of partially oxidized carbon compounds in the urine and have come to the conclusion that this factor is negligible. The entire absence of abnormal respiratory quotients supports this view. The lowest quotient found was 0.72, the highest 1.04, obtained respectively during fasting and high carbohydrate ingestion, and thus exhibiting entirely normal relations.

The most uncertain factor is the variation in heat production caused by changes in the muscular activity. It is quite possible that a patient who is very delirious and very restless might produce twice as many calories as when quiet. The total heat production of such patients could be determined only by the Middletown type of experiment in which the subject was kept in a respiration calorimeter for days at a time. Such experiments are obviously impossible in typhoid fever. The question remains as to whether we obtain a fair sample of the day's metabolism by making two or three observations a week between the hours of 11 in the morning and 2 or 3 o'clock in the afternoon. This period includes some of the morning hours when the metabolism is said to be low and some of the afternoon hours when it is said to be high. During the experiment the activity of the patient has been almost the same as the activity observed in the ward during the greater part of the day between the hours of 5 in the morning and 8 in the evening. In the calorimeter the subjects are allowed to turn from side to side several times during the hour and they shift their position often enough to make themselves comfortable, which is exactly what they do in their beds in the ward. Part of the time they doze and part of the time they are awake and are looking out of the calorimeter window. In the ward they are kept flat in bed and are never allowed to sit up until the temperature has been normal for several days. They are never given cold tubs and hardly ever given cold sponges. Their food is served on trays and they help themselves with a minimum of exertion. In the morning the nurse gives each patient an enema, sponges

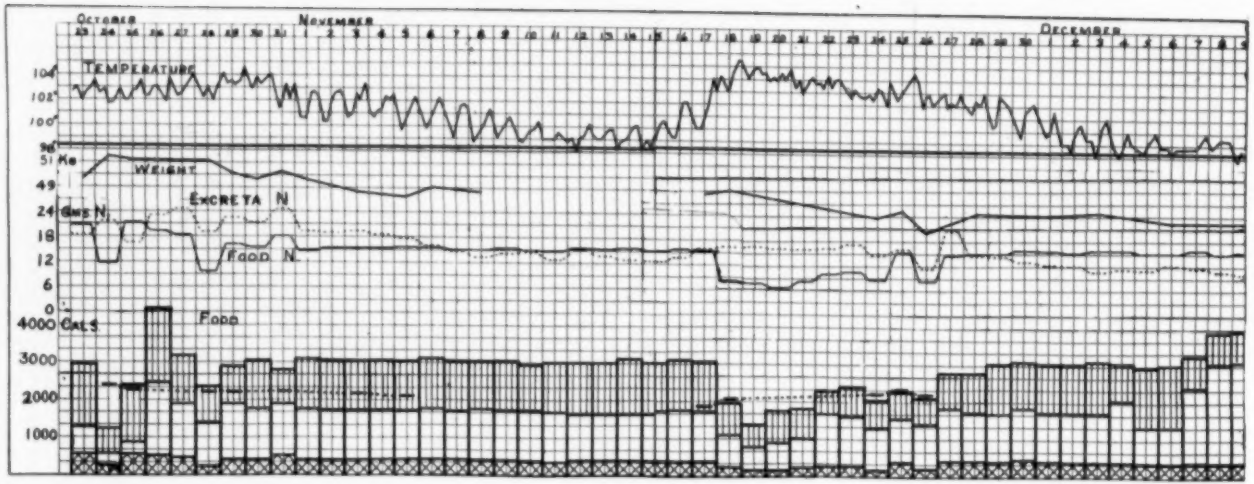


Chart 3.—Part 1

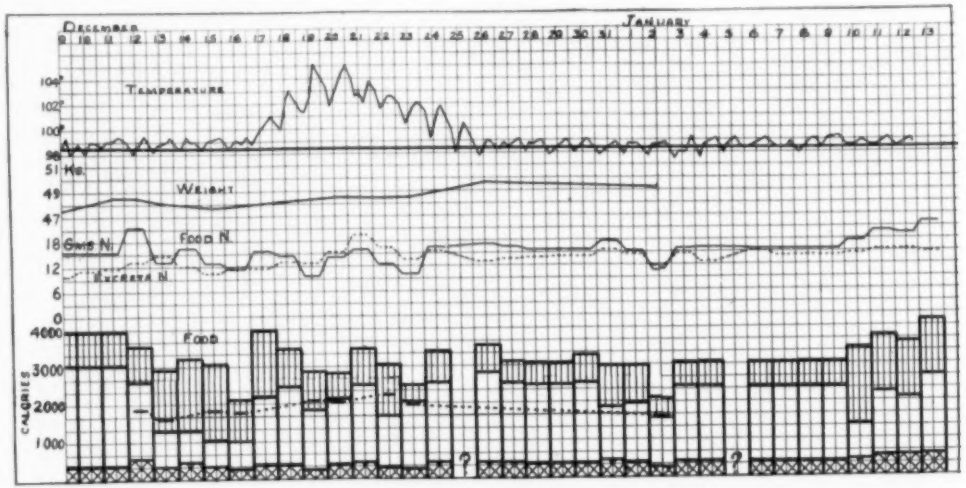


Chart 3.—Part 2

Chart 3.—Morris S.—Temperature, body weight. Food nitrogen, continuous line; excreta nitrogen, dotted line. At the base of the chart, columns representing total calories of food. Protein calories, crossed diagonals — fat calories, blank — carbohydrate calories, vertical lines. The dot-dash line represents the estimated heat production in calories for twenty-four hours. The dashes are placed on days of the observations in the calorimeter. Note that the calories of the food exceed the estimated heat production except for a period during the first relapse. Food was not measured on December 25th and January 5th.

him off with warm water, slides him from his bed to the weighing platform, makes up his bed and slides him back again. During the rest of the day he is seldom disturbed and he spends his time dozing, reading or talking with his neighbors. A few of the patients have been mildly irrational for a few days at a time and such occurrences have been noted in detail in the histories. Subsultus tendinum and jactitation have rarely been observed. On the other hand, there must be a reduction of the metabolism at night since the patients sleep soundly and are seldom disturbed. In a previous paper we have estimated that the bodily activity increases the metabolism during the whole day to an average of 10 per cent. above its basal metabolism. Since that time we have had the opportunity of making two observations on patients who were irrational and restless. November 3 Morris S. was in the calorimeter for three hours. During the first hour he was unusually quiet, during the second hour he was restless and tossed about the bed, during the third hour he was evidently irrational, tossed about and wrote three or four long notes which he held up to the calorimeter window to tell us about the animals that were biting him with their sharp teeth.

In spite of this unusual activity his metabolism during the three hour period was only 43 per cent. above the normal and was only 5 per cent. higher than during the quiet basal observation made two days later, when the temperature was lower. Edward B. on Nov. 10, 1914, was in the calorimeter with a temperature of 40.3 C., and during the second and third hours was restless and mildly irrational. His heat production was only 51 per cent. above the average normal. These two observations, which are fair samples of the severest symptoms observed in the typhoid patients presented in this paper, do not indicate any unusual degree of increase of heat production from the moderate activity. There may be an uneconomical expenditure of energy in typhoid in the performance of a certain task but even so the total expenditure is not great in these cases. It is hoped that at a later date the question of muscular efficiency in fever may be solved by having typhoid patients and normal controls do a stated amount of work on an ergometer while in the calorimeter.

A detailed consideration of all the factors is of importance when one attempts to draw conclusions from a discrepancy between the calculated intake and the calculated output. It is necessary to consider the possible errors in the various determinations and it is necessary to select somewhat arbitrary average percentages for the various factors. The measurement of the food intake is unusually accurate. Most of

the foods such as cereals, bread, sugars, egg white and egg yolk, butter and crackers vary but slightly from the samples analyzed. The other foods given, such as milk, cream, and dried apples are not subject to large enough variations to affect the results. Foods subject to significant variations are carefully avoided.

The methods of preparation and weighing have been described in another paper and they are believed to be accurate within 2 per cent. It is doubtful if this error combined with the error in the variation of the individual foods exceeds plus or minus 5 per cent. and there is no factor to throw the error on one side of the scale more often than on the other. The heat production of the patients as determined by the method of indirect calorimetry is not subject to an error of more than 1 or 2 per cent. on the average, although it is possible that some individual observations may show an error of 5 per cent. The collection of the twenty-four hour specimens of urine and the estimation of

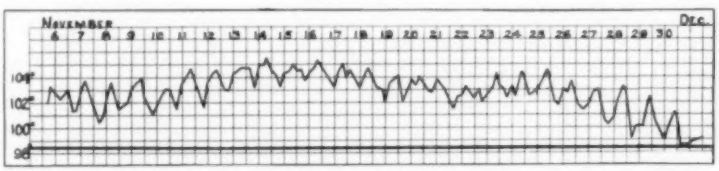


Chart 4.—Charles F. Temperature curve.

the nitrogen are so carefully controlled by duplicate analyses and checks in the collection of specimens and in the calculations that there is no chance for an error greater than 1 per cent. In the cases in which the feces were not analyzed the method of estimating the feces nitrogen as 10 per cent. of the food nitrogen gives a plus or minus error of less than half a gram a day while there is possibly as great an error in the fact that we do not take into account the nitrogen losses through the skin.

In order to estimate the caloric output of typhoid patients on whom respiration experiments were made, one can add to the basal metabolism on average 3 per cent. for the specific dynamic action of the food and 10 per cent. for muscular activity. We can, therefore, calculate with reasonable accuracy the heat production for the day by adding 13 per cent. to the figures obtained in the febrile basal experiments and 10 per cent. to the figures obtained in the experiments after food. In the cases in which several observations were made it seems fair to plot a smooth curve and consider that the heat production of the non-experi-

mental days was the same as on the days in which actual determinations were made.

If we look now at Table 4 and Charts (3), (6) and (8), it becomes evident that three of the patients reported in this paper and one reported in a previous paper[1] showed a distinct negative nitrogen balance when they were receiving considerably more calories than were sufficient to cover the calculated heat production. A glance at the food charts will show that the typhoid patients were given 12 to 16 grams of nitrogen a day and that the proportions of fat and carbohydrate were well balanced. The only criticism of the manner of feeding is that on the days of the basal determinations it was necessary for the patient to fast sixteen to twenty hours. One might expect a slight negative nitrogen balance at such times, but this should be offset by a positive balance the next day. As a matter of fact the negative balance is not much greater on the experi-

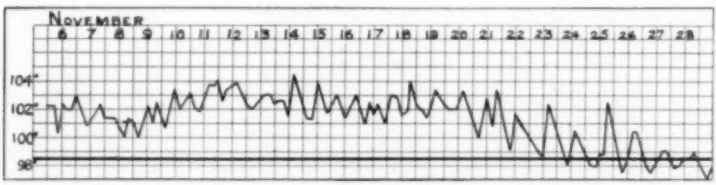


Chart 5.—Howard F. Temperature curve.

mental days. Moreover, as was pointed out in the previous paper, many patients who have not been the subject of respiration experiments have shown a persistent negative nitrogen balance on a diet much greater than the estimated heat production and have not come into nitrogen equilibrium until the theoretical requirement was exceeded by from 50 to 110 per cent.

In another place[1] when touching on this subject we referred to the possibility of a storage of fat while there was a negative nitrogen balance and loss of body weight. The body weight is notoriously a poor index of gain or loss of body tissue except in long periods of observation. The body changes its content of water so easily and so rapidly with changing diets and changing periods of the disease that it would be very easy to store 1 or 2 kilograms of fat without noticeable effect on the weight. We must remember that 1 kilogram of fat represents about 9,300 calories. Even without assuming a change in the water concentration of the body, it is possible to account for the storage of the excess calories. In the tables one can find several periods of almost con-

stant body weight when the patient was losing nitrogen. If we consider that for every 3 grams of nitrogen lost the patient loses about 100 grams of muscle tissue, it is possible to calculate the total muscle tissue lost. If this were replaced by fat the weight would remain constant and the storage of the excess calories could easily be accounted for. For example, Morris S. between October 23 and November 3 lost about 1,770 grams of muscle tissue, which could be replaced by enough fat to represent 15,900 calories.

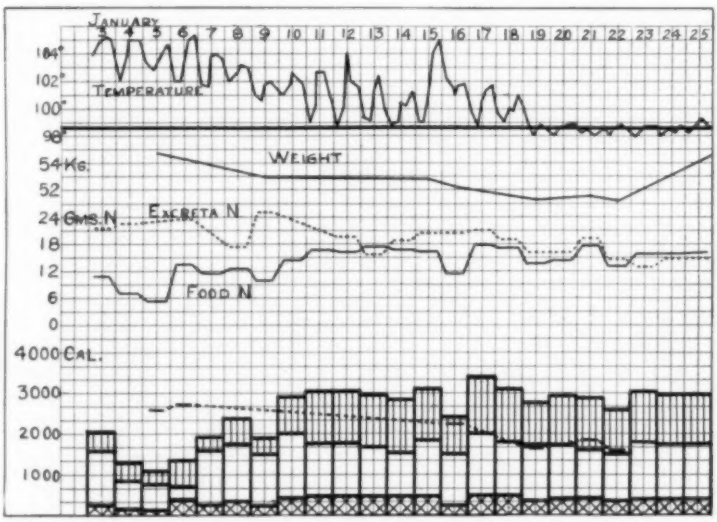


Chart 6.—Karl S. Temperature and body weight. Food nitrogen, continuous line; excreta nitrogen, dotted line. The columns at base represent calories in food. Protein calories crossed diagonals, fat calories blank, carbohydrate calories vertical lines. Dot-dash line represents the estimated heat production in calories for twenty-four hours, dashes being placed on the days of the calorimeter observations. Note the negative balance during the last days of the fever when the patient was receiving in food more calories than the estimated heat production.

In none of the cases were the protein and carbohydrate calories together sufficient to cover the heat production, so it is not necessary to assume the transformation of carbohydrate into fat, although we have shown that this is possible during fever in one patient[1] (Salvatore L.).

*The Toxic Destruction of Protein.*—The proof of the fact that typhoid patients show a negative nitrogen balance on a diet which furnishes more calories than the heat production, is perhaps the most

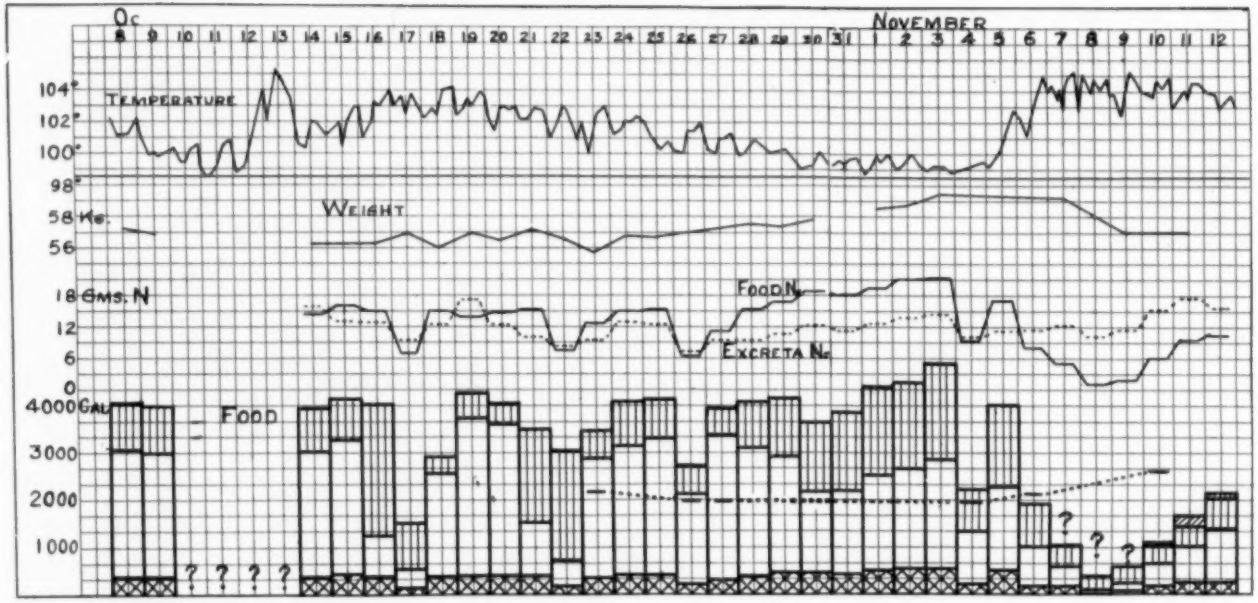


Chart 7.—Edward B. Temperature, body weight, food and excreta nitrogen. Food calories and dot-dash line representing estimated heat production. On November 7th, 8th and 9th, patient vomited, making measurement of food intake somewhat inaccurate. November 10th, 11th and 12th he received some alcohol calories.

important piece of evidence which has yet been presented in the discussion of the so-called toxic destruction of protein. Clinicians have long been aware of the large excretion of nitrogen in fever and have attributed it to an abnormal destruction of protein caused by the toxins of the disease. It is not necessary in this connection to review the older clinical work, since that is admirably presented in the standard discus-

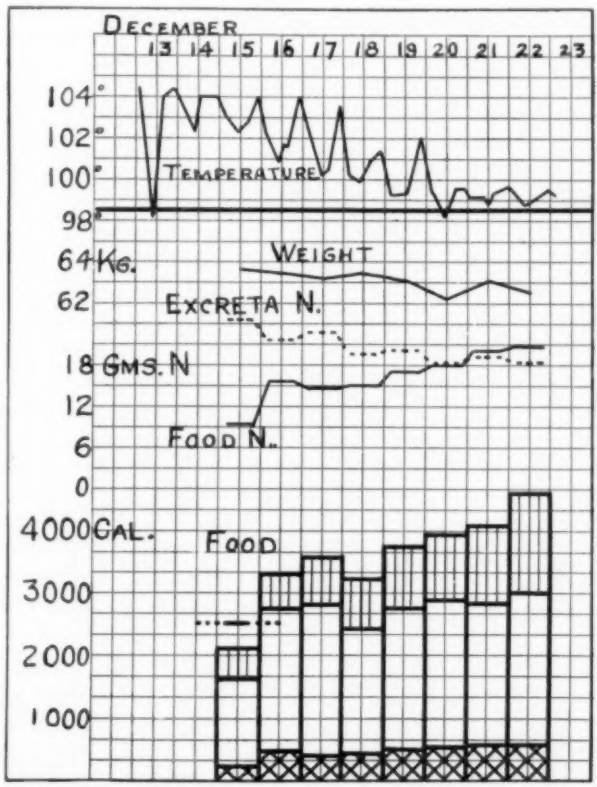


Chart 8.—John K. Temperature, body weight, food and excreta nitrogen. Food calories and dot-dash line showing estimated heat production.

sions of metabolism in fever. The results of the large number of investigations made on lower animals, while important, cannot with certainty be transferred to man.

The question of the toxic destruction of protein took on a new aspect when in 1909 Shaffer and Coleman[6] showed that it was possible

to obtain nitrogen balance in typhoid patients, even during the second and third weeks of the disease. This they accomplished only by making the total caloric value of the food very high, from 60 to 90 calories per kilogram, and the food nitrogen from 9 to 15 grams. In their discussion of the results they expressed the opinion that "....it is perhaps improbable that the total heat production reached the values represented by the larger amounts of food." This work proved that there was no toxic destruction in the sense of a nitrogen loss which could not be counterbalanced by the nitrogen intake.

The question of the average heat production of typhoid patients was fully discussed in last year's paper[1] and attention was drawn to the fact that typhoid patients did not come into nitrogen equilibrium until their theoretical caloric requirement was exceeded by from 50 to 110 per cent. Grafe[10] in 1911 had shown that his typhoid patients when studied in a respiration chamber, ten to sixteen hours after their last meal, derived about 10 to 20 per cent. of their calories from protein, a percentage usually found in normal men. From this Grafe concluded that he had shown that the protein metabolism in fever was not abnormal. The percentage of calories derived from protein on the first eighteen hours after food ingestion depends largely on the previous level of the protein metabolism. Normal individuals who have been taking 15 to 19 grams of nitrogen a day will naturally derive about 15 to 20 per cent. of their calories from protein as is shown in Paper 4 of this series. Normal individuals who have been maintaining themselves in nitrogen balance on 4 to 5 grams a day will derive only 5 per cent. of their calories from protein. The comparison should have been made between normal men and typhoid patients while both were on their nitrogen minima. This will be shown later in a discussion of Kocher's work.

Rolland[11] working under Grafe's direction brought several fever patients into nitrogen balance by means of a caloric intake which she believed to be equal to the heat production as estimated from the averages of other patients. Respiration experiments were not made on the patients themselves. Our reasons for believing that the food intake was above the requirement have been set forth in another place[1] (p. 38).

Recent work from Friedrich Müller's clinic has thrown important light on the subject. Graham and Poulton[12] established themselves

10. Grafe E.: Untersuchungen über den Stoff- und Kraftwechsel im Fieber, Deutsch. Arch. f. klin. Med., 1911, ci, 209.

11. Rolland, Anne: Zur Frage des toxogenen Eiweisszerfalls im Fieber des Menschens, Deutsch. Arch. f. klin. Med., 1912, cvii, 440.

12. Graham and Poulton: Influence of Temperature on Protein Metabolism, Quart. Jour. Med., 1912, vi, 82.

on a minimal nitrogen elimination of 4 to 5 grams a day and found no increase in the elimination when they raised their temperatures to about 40 C. by means of a steam bath. Kocher[13] in two normal subjects established a nitrogen minimum at a similar level and found no increase when he raised the heat production by means of a 60 kilometer walk. All of these experiments were made on a caloric intake calculated to cover the requirement. They indicate that rise in temperature alone or increase in heat production alone will not cause an increased protein metabolism, at least when applied for a portion of one day. Kocher then attempted by means of a diet amply sufficient to cover the calculated requirement to bring down the nitrogen elimination of fever patients to the low level obtained in normal men. This he found to be impossible until the active stage of the disease was passed. Grafe[14] in a recent paper has criticized these experiments.

To all of the patients in Table 4 food was given which had an energy content much greater than the amount required by the patients as measured directly when they were in the calorimeter. Although the protein content of the diet, as represented by an intake of 15 grams of nitrogen, was ample to establish nitrogen equilibrium had the diet been given to normal men, it did not accomplish this in typhoid fever. It is difficult to see in this anything except the proof that there is an abnormal destruction of protein in typhoid fever. In some cases the protein destruction continued several days after the temperature had reached a low level. It is impossible to escape the conclusion that the destruction of protein is caused by the toxins of the disease.

## SUMMARY AND CONCLUSIONS

The heat production of typhoid patients has been measured by the methods of direct and indirect calorimetry in a series of sixty-one experiments. The two methods agreed closely, the total divergence being 2.2 per cent. and the average divergence in the individual experiments being 5 per cent. This and the entire absence of abnormal respiratory quotients indicate that in typhoid fever protein, fat and carbohydrate are oxidized to the same or approximately the same end products as in health, and in their oxidation give off the standard

13. Kocher, Rudolph A.: Ueber die Grosse des Eiweisszerfalls bei Fieber und bei Arbeitsleitstung, Deutsch. Arch. f. klin. Med., 1914, cxv, 82.

14. Grafe, E.: Zur Genese des Eiweisszerfalls im Fieber, Deutsch. Arch. f. klin. Med., 1914, cvi, 328.

TABLE 5.—CLINICAL—

| Subject Date Weight | Period | End of Period | Carbon-dioxid, Gm. | Oxygen, Gm. | R. Q. | Water, Gm. | Urine N per Hour, Gm. | Indirect Calo-rimetry, Cal. | Heat Elimi-nated, Cal. | Direct Calo-rimetry (Rectal Temp.) Cal. | Rectal Temp. C. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Morris S. ..... Oct. 24, '13 51.50 kg. | Prelim. | 11:35 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 39.86 |
| | 1 | 12:35 | 30.06 | 30.02 | .73 | 47.84 | 0.713 | 97.09 | 83.41 | 84.28 | 39.95 |
| | 2 | 1:35 | 27.92 | 28.13 | .77 | 46.72 | 0.713 | 85.89 | 84.66 | 81.00 | 39.89 |
| | 3 | 2:35 | 26.20 | 24.04 | .79 | 39.48 | 0.713 | 79.28 | 74.63 | 85.72 | 40.17 |
| Morris S. ..... Oct. 25, '13 51.22 kg. | Prelim. | 11:00 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 39.21 |
| | 1 | 12:00 | 29.05 | 26.82 | .80 | 42.10 | 0.671 | 88.95 | 78.03 | 90.06 | 39.49 |
| | 2 | 1:00 | 28.68 | 25.87 | .81 | 39.10 | 0.671 | 85.77 | 80.11 | 86.09 | 39.69 |
| | 3 | 2:00 | 31.75 | 25.46 | .91 | 42.82 | 0.671 | 86.62 | 90.07 | 78.55 | 39.49 |
| Morris S. ..... Oct. 28, '13 51.50 kg. | Prelim. | 11:10 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 39.62 |
| | 1 | 12:10 | 34.12 | 28.35 | .88 | 43.31 | 0.732 | 95.71 | 92.00 | 75.53 | 39.27 |
| | 2 | 1:10 | 32.64 | 24.82 | .96 | 42.41 | 0.732 | 85.31 | 94.67 | 76.33 | 38.87 |
| | 3 | 2:10 | 30.25 | 22.80 | .96 | 39.40 | 0.732 | 78.60 | 86.73 | 84.65 | 38.81 |
| | 4 | 3:10 | 29.93 | 24.33 | .90 | 34.39 | 0.732 | 82.34 | 78.47 | 93.97 | 39.20 |
| | 5 | 4:10 | 28.28 | 22.05 | .94 | 31.75 | 0.732 | 74.50 | 74.35 | 90.84 | 39.65 |
| Morris S. ..... Oct. 29, '13 49.86 kg. | Prelim. | 11:10 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 39.63 |
| | 1 | 12:10 | 26.73 | 23.77 | .82 | 33.11 | 0.658 | 79.00 | 81.19 | 76.49 | 39.50 |
| | 2 | 1:10 | 27.49 | 25.05 | .77 | 34.03 | 0.658 | 85.28 | 84.48 | 85.73 | 39.54 |
| Morris S. ..... Oct. 31, '13 50.28 kg. | Prelim. | 11:00 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 39.06 |
| | 1 | 12:00 | 28.95 | 25.45 | .83 | 32.13 | 1.056 | 84.11 | 74.09 | 58.27 | 38.94 |
| | 2 | 1:00 | 29.09 | 24.17 | .80 | 36.41 | 1.056 | 81.15 | 79.19 | 79.96 | 39.08 |
| | 3 | 2:00 | 29.57 | 26.58 | .80 | 36.76 | 1.056 | 87.80 | 77.70 | 87.13 | 39.43 |
| Morris S. ..... Nov. 3, '13 48.53 kg. | Prelim. | 10:30 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 38.63 |
| | 1 | 11:30 | 24.91 | 20.42 | .89 | 28.58 | 0.499 | 69.30 | 56.44 | 72.99 | 39.05 |
| | 2 | 12:30 | 28.70 | 26.23 | .80 | 33.10 | 0.499 | 83.77 | 74.39 | 77.80 | 39.15 |
| | 3 | 1:30 | 27.53 | 27.90 | .72 | 42.11 | 0.499 | 90.92 | 86.25 | 71.74 | 38.81 |
| Morris S. ..... Nov. 5, '13 48.45 kg. | Prelim. | 11:20 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 38.08 |
| | 1 | 12:20 | 25.42 | 23.10 | .80 | 29.99 | 0.491 | 76.79 | 77.98 | 81.34 | 38.19 |
| | 2 | 1:20 | 26.42 | 23.05 | .83 | 38.62 | 0.491 | 77.19 | 74.75 | 67.00 | 38.01 |
| | 3 | 2:20 | 25.00 | 23.65 | .79 | 30.13 | 0.491 | 78.29 | 72.89 | 75.34 | 38.10 |
| Morris S. ..... Nov. 17, '13 47.99 kg. | Prelim. | 11:10 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 38.48 |
| | 1 | 12:10 | 21.90 | 19.01 | .84 | 24.39 | 0.336 | 63.87 | 57.98 | 62.77 | 38.61 |
| | 2 | 1:10 | 23.56 | 20.82 | .82 | 24.44 | 0.336 | 69.76 | 60.70 | 69.71 | 38.82 |
| | 3 | 2:10 | 23.79 | 22.28 | .78 | 26.06 | 0.336 | 73.79 | 66.08 | 72.85 | 39.00 |
| Morris S. ..... Nov. 18, '13 48.77 kg. | Prelim. | 11:00 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 39.72 |
| | 1 | 12:00 | 24.40 | 22.01 | .81 | 26.55 | 0.567 | 73.01 | 67.36 | 64.94 | 39.67 |
| | 2 | 1:00 | 26.37 | 21.33 | .90 | 28.15 | 0.567 | 72.56 | 71.65 | 82.60 | 39.98 |
| | 3 | 2:00 | 25.91 | 23.57 | .80 | 28.88 | 0.567 | 78.11 | 72.05 | 77.47 | 40.15 |
| Morris S. ..... Nov. 24, '13 46.60 kg. | Prelim. | 11:13 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 39.54 |
| | 1 | 12:13 | 29.17 | 25.27 | .78 | 29.24 | 0.514 | 83.56 | 67.50 | 68.12 | 39.59 |
| | 2 | 1:13 | 26.91 | 24.54 | .75 | 32.68 | 0.514 | 85.96 | 75.16 | 64.72 | 39.33 |
| | 3 | 2:13 | 26.41 | 25.48 | .75 | 35.00 | 0.514 | 83.64 | 80.48 | 73.52 | 39.16 |

| Surface Temp., C. | Average Pulse | Work Adder., Cm. | Non-Protein, R. Q. | Per Cent. Calories from | | | Calories Per Hour | | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Protein | Fat | Carbohyd. | Per Kg. | Per Sq. M. | |
| ..... | 96(?) | 36.0 | .71 | 24 | 75 | 1 | 1.90 | 57.33 | Basal. |
| ..... | 96 | 21.0 | .77 | 28 | 58 | 14 | 1.67 | 50.40 | |
| ..... | 105 | 17.0 | .79 | 31 | 49 | 20 | 1.54 | 46.53 | |
| ..... | 101 | 30.0+ | .80 | 20 | 54 | 26 | 1.74 | 52.36 | 9:30-10:00 a. m., protein meal. 9.0 gm. N. |
| ..... | 98 | 21.5 | .81 | 21 | 52 | 27 | 1.68 | 50.48 | |
| ..... | 105 | 18.0++ | .94 | 21 | 17 | 62 | 1.69 | 50.98 | |
| ..... | 119 | 35.0 | .90 | 20 | 29 | 51 | 1.88 | 66.70 | At 10:22, 115 gm. com. glucose = 100 gm. dextrose. Asleep from 3-3:40. |
| ..... | 113 | 25.0+5? | 1.01 | 23 | .. | 77 | 1.68 | 50.54 | |
| ..... | 108 | 30.5 | 1.02 | 25 | .. | 75 | 1.55 | 46.56 | |
| ..... | 108 | 18.0 | .93 | 24 | 19 | 57 | 1.62 | 48.78 | |
| ..... | 107 | 9.0 | .99 | 26 | 3 | 71 | 1.47 | 44.19 | |
| ..... | 105 | 24.0 | .82 | 22 | 47 | 31 | 1.58 | 47.17 | Basal. |
| ..... | 106 | 17.5 | .76 | 20 | 65 | 15 | 1.70 | 50.91 | |
| ..... | 101 | 10.0 (?) | .84 | 33 | 36 | 31 | 1.68 | 50.16 | 8:40-9:20, protein meal; 10.3 gm. N. |
| ..... | 102 | 11.2+ | .96 | 35 | 12 | 53 | 1.62 | 48.39 | |
| ..... | 98 | 9.5 | .81 | 32 | 44 | 24 | 1.74 | 52.18 | |
| ..... | 106 | 11.7 | .91 | 19 | 25 | 56 | 1.42 | 42.09 | Basal. 1st. hr. quiet, 2d. hr. restless, 3d. hr. restless; wrote 3 or 4 notes. |
| ..... | 111 | 32.0 | .79 | 16 | 59 | 25 | 1.71 | 50.96 | |
| ..... | 106 | 8.0+ | .70 | 15 | 85 | .. | 1.86 | 55.30 | |
| ..... | 98 | 9.5 | .80 | 17 | 56 | 27 | 1.58 | 46.89 | Basal. |
| ..... | 109 | 8.0 | .84 | 17 | 45 | 38 | 1.59 | 47.18 | |
| ..... | 112 | 8.0 | .78 | 17 | 61 | 22 | 1.62 | 47.86 | |
| 37.29 | | | | | | | | | |
| 37.52 | 100 | 11.0 | .84 | 14 | 45 | 41 | 1.33 | 39.28 | Basal. |
| 37.83 | 113 | 6.8 | .83 | 13 | 51 | 36 | 1.45 | 42.90 | |
| 37.94 | 112 | 3.0 | .77 | 12 | 68 | 20 | 1.54 | 45.38 | |
| 38.89 | | | | | | | | | |
| 38.98 | 114 | 0.3 | .81 | 21 | 52 | 27 | 1.50 | 44.44 | Basal. |
| 39.27 | 117 | 14.7 | .92 | 21 | 20 | 59 | 1.49 | 44.16 | |
| 39.16 | 124 | 13.7 | .80 | 19 | 55 | 26 | 1.60 | 47.54 | |
| ..... | ... | 12.0 | .78 | 16 | 64 | 20 | 1.77 | 52.32 | Basal. |
| ..... | 122 | 0.0 | .74 | 16 | 73 | 11 | 1.81 | 53.39 | |
| ..... | 126 | 0.5 | .74 | 16 | 73 | 11 | 1.78 | 52.37 | |

TABLE 5.—CLINICAL CALORIMETRY—

| Subject Date Weight | Period | End of Period | Carbon-dioxid, Gm. | Oxygen, Gm. | R. Q. | Water, Gm. | Urine N per Hour, Gm. | Indirect Calorimetry, Cal. | Heat Eliminated, Cal. | Direct Calorimetry (Rectal Temp.) Cal. | Rectal Temp. C. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Morris S. ..... Nov. 25, '13 47.24 kg. | Prelim. | 11:20 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 39.40 |
| | 1 | 12:20 | 28.17 | 24.45 | .84 | 29.86 | 0.618 | 81.79 | 71.80 | 66.06 | 39.30 |
| | 2 | 1:20 | 30.38 | 26.92 | .82 | 47.61 | 0.618 | 89.78 | 91.51 | 78.22 | 38.97 |
| | 3 | 2:20 | 29.20 | 27.94 | .78 | 48.78 | 0.618 | 89.93 | 88.95 | 95.35 | 39.13 |
| Morris S. ..... Nov. 26, '13 46.11 kg. | Prelim. | 10:50 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 39.61 |
| | 1 | 11:50 | 26.29 | 24.80 | .77 | 27.88 | 0.329 | 82.10 | 69.08 | 52.60 | 39.19 |
| | 2 | 12:50 | 25.68 | 24.64 | .76 | 34.79 | 0.329 | 81.28 | 70.19 | 71.14 | 38.99 |
| | 3 | 1:50 | 25.70 | 24.85 | .75 | 42.13 | 0.329 | 81.84 | 68.38 | 79.59 | 38.77 |
| Morris S. ..... Dec. 12, '13 48.61 kg. | Prelim. | 10:56 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 37.01 |
| | 1 | 11:56 | 23.45 | 20.22 | .84 | 18.48 | 0.272 | 68.20 | 61.73 | 53.71 | 36.82 |
| | 2 | 12:56 | 22.88 | 20.96 | .83 | 21.26 | 0.272 | 70.44 | 64.58 | 69.48 | 36.95 |
| | 3 | 1:56 | 24.99 | 21.42 | .85 | 24.01 | 0.272 | 72.36 | 66.64 | 69.52 | 37.08 |
| Morris S. ..... Dec. 13, '13 48.07 kg. | Prelim. | 10:36 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 37.07 |
| | 1 | 11:36 | 18.99 | 16.89 | .82 | 18.84 | 0.322 | 56.39 | 58.07 | 50.93 | 36.90 |
| | 2 | 12:36 | 20.10 | 17.29 | .85 | 19.31 | 0.322 | 58.16 | 58.63 | 63.06 | 37.02 |
| | 3 | 1:36 | 20.76 | 18.90 | .89 | 20.26 | 0.322 | 62.88 | 61.95 | 63.59 | 37.07 |
| Morris S. ..... Dec. 15, '13 48.17 kg. | Prelim. | 10:52 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 37.30 |
| | 1 | 11:52 | 24.51 | 18.29 | .98 | 18.41 | 0.384 | 63.45 | 58.74 | 47.60 | 37.03 |
| | 2 | 12:52 | 26.76 | 18.98 | 1.03 | 20.90 | 0.384 | 66.42 | 63.52 | 64.97 | 37.10 |
| | 3 | 1:52 | 26.83 | 18.82 | 1.04 | 22.07 | 0.384 | 65.97 | 64.19 | 67.97 | 37.23 |
| Morris S. ..... Dec. 16, '13 47.86 kg. | Prelim. | 11:06 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 37.22 |
| | 1 | 12:06 | 22.51 | 17.81 | .92 | 20.82 | 0.299 | 61.10 | 63.36 | 61.62 | 37.30 |
| | 2 | 1:06 | 21.91 | 18.33 | .87 | 21.42 | 0.299 | 62.12 | 62.76 | 63.36 | 37.33 |
| | 3 | 2:06 | 22.37 | 19.33 | .84 | 21.79 | 0.299 | 65.08 | 63.87 | 60.35 | 37.25 |
| Morris S. ..... Dec. 19, '13 48.74 kg. | Prelim. | 11:10 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 39.19 |
| | 1 | 12:10 | 27.38 | 21.99 | .91 | 22.55 | 0.403 | 74.94 | 70.40 | 67.95 | 39.14 |
| | 2 | 1:10 | 30.04 | 22.70 | .96 | 25.64 | 0.403 | 78.51 | 75.00 | 84.00 | 39.41 |
| | 3 | 2:10 | 29.47 | 23.51 | .91 | 27.26 | 0.403 | 80.32 | 74.21 | 87.13 | 39.75 |
| Morris S. ..... Dec. 20, '13 48.52 kg. | Prelim. | 10:40 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 39.29 |
| | 1 | 11:40 | 23.69 | 22.51 | .77 | 23.81 | 0.547 | 73.93 | 67.11 | 76.26 | 39.53 |
| | 2 | 12:40 | 25.60 | 23.42 | .80 | 25.60 | 0.547 | 77.57 | 70.95 | 78.45 | 39.76 |
| | 3 | 1:40 | 25.51 | 23.84 | .78 | 27.47 | 0.547 | 78.68 | 72.88 | 72.56 | 39.77 |
| Morris S. ..... Dec. 22, '13 48.87 kg. | Prelim. | 11:16 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 38.65 |
| | 1 | 12:36 | 37.28 | 28.77 | .94 | 37.28 | 0.705 | 98.85 | 97.57 | 112.20 | 39.05 |
| | 2 | 1:36 | 38.84 | 22.32 | .94 | 28.28 | 0.529 | 76.65 | 73.08 | 88.65 | 39.47 |
| | 3 | 2:36 | 28.86 | 22.21 | .95 | 29.24 | 0.529 | 76.39 | 74.60 | 78.88 | 39.59 |
| Morris S. ..... Dec. 23, '13 48.60 kg. | Prelim. | 11:06 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 38.04 |
| | 1 | 12:06 | 23.51 | 21.45 | .80 | 25.82 | 0.428 | 71.21 | 68.75 | 73.19 | 38.16 |
| | 2 | 1:06 | 23.94 | 21.92 | .80 | 25.39 | 0.428 | 72.73 | 70.84 | 80.86 | 38.46 |
| | 3 | 2:06 | 24.35 | 22.79 | .78 | 25.38 | 0.428 | 75.32 | 69.85 | 76.84 | 38.66 |
| Morris S. ..... Jan. 2, '14 49.26 kg. | Prelim. | 11:16 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 36.97 |
| | 1 | 12:16 | 19.10 | 16.62 | .84 | 19.75 | 0.386 | 55.63 | 58.53 | 52.15 | 36.85 |
| | 2 | 1:16 | 19.27 | 17.07 | .82 | 20.20 | 0.386 | 56.94 | 57.89 | 64.93 | 37.05 |
| | 3 | 2:16 | 19.80 | 18.38 | .78 | 22.05 | 0.386 | 60.77 | 61.54 | 60.88 | 37.07 |

—IN TYPHOID FEVER—(*Continued*)

| Surface Temp., C. | Average Pulse | Work Adder., Cm. | Non-Protein, R. Q. | Per Cent. Calories from | | | Calories Per Hour | | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Protein | Fat | Carbohyd. | Per Kg | Per Sq. M. | |
| 38.37 | | | | | | | | | |
| 38.66 | 112 | 18.5 | .85 | 20 | 42 | 38 | 1.72 | 50.83 | 9.35:10:15, protein meal; 8.7 gm. N. Began to sweat at end of second hour. |
| 38.12 | 122 | 12.2 | .83 | 18 | 49 | 33 | 1.89 | 55.80 | |
| 37.76 | 119 | 9.5 | .78 | 18 | 62 | 20 | 1.90 | 55.89 | |
| 38.87 | | | | | | | | | |
| 38.59 | 112 | 5.5 | .77 | 11 | 70 | 19 | 1.79 | 51.83 | Basal. Patient restless in second period. |
| 38.18 | 119 | 11.0+ | .75 | 11 | 75 | 14 | 1.77 | 51.31 | |
| 37.53 | 123 | 12.0 | .75 | 11 | 77 | 12 | 1.78 | 51.67 | |
| 35.60 | | | | | | | | | |
| 35.52 | 91 | 3.8 | .85 | 11 | 46 | 43 | 1.40 | 41.59 | 9:03-9:30, protein meal; 10.6 gm. N. |
| 35.69 | 94 | 18.6 | .83 | 10 | 51 | 39 | 1.45 | 42.95 | |
| 35.73 | 98 | 14.5 | .85 | 10 | 45 | 45 | 1.49 | 44.12 | |
| 35.82 | | | | | | | | | |
| 35.64 | 74 | 9.0 | .82 | 15 | 52 | 33 | 1.17 | 34.64 | Basal. Asleep in first period. |
| 35.82 | 88 | 9.2 | .85 | 15 | 43 | 42 | 1.21 | 35.73 | |
| 35.98 | 87 | 7.5 | .80 | 14 | 59 | 27 | 1.31 | 38.62 | |
| 35.98 | | | | | | | | | |
| 35.54 | 83 | 6.0 | 1.01 | 16 | .. | 84 | 1.32 | 38.95 | At 10:13, 115 gm. commercial glucose. |
| 35.72 | 102 | 5.1 | 1.07 | 15 | .. | 85 | 1.38 | 40.77 | |
| 35.75 | 100 | 1.2 | 1.09 | 15 | .. | 85 | 1.37 | 40.50 | |
| 35.99 | | | | | | | | | |
| 35.93 | 84 | 5.7 | .94 | 13 | 18 | 69 | 1.28 | 37.65 | Basal. |
| 35.95 | 87 | 2.5 | .88 | 13 | 35 | 52 | 1.30 | 38.27 | |
| 36.00 | 93 | 7.0 | .85 | 12 | 46 | 42 | 1.36 | 40.10 | |
| 37.52 | | | | | | | | | |
| 37.29 | 105 | 0.3 | .93 | 17 | 20 | 63 | 1.54 | 45.64 | At 10:26, 115 gm. commercial glucose. |
| 37.64 | 121 | 7.3 | 1.00 | 17 | 1 | 82 | 1.61 | 47.81 | |
| 37.71 | 121 | 2.0 | .94 | 16 | 19 | 65 | 1.65 | 48.92 | |
| 37.49 | | | | | | | | | |
| 37.59 | 108 | 1.6 | .76 | 20 | 67 | 13 | 1.55 | 45.13 | Basal. |
| 37.87 | 114 | 8.1 | .79 | 19 | 57 | 24 | 1.63 | 47.36 | |
| 37.91 | 117 | 2.2 | .77 | 18 | 64 | 18 | 1.65 | 48.00 | |
| 36.85 | | | | | | | | | |
| 37.44 | 109 | 9.2 | .98 | 19 | 6 | 75 | 1.52 | 45.07 | At 10:24, 115 gm. commercial glucose. First period 1 hr. 20 min. because patient moved at end of hour. |
| 37.67 | 120 | 6.5 | .97 | 18 | 8 | 74 | 1.57 | 46.61 | |
| 37.71 | 120 | 1.2 | .98 | 18 | 6 | 76 | 1.57 | 46.44 | |
| 36.64 | | | | | | | | | |
| 36.62 | 99 | 1.2 | .80 | 16 | 58 | 26 | 1.46 | 43.42 | Basal. |
| 36.80 | 100 | 9.2 | .79 | 16 | 59 | 25 | 1.50 | 44.35 | |
| 37.07 | 105 | 4.0 | .77 | 15 | 66 | 19 | 1.55 | 45.93 | |
| 35.49 | | | | | | | | | |
| 35.57 | 69 | 8.8 | .84 | 18 | 44 | 38 | 1.13 | 33.63 | Basal. |
| 35.57 | 76 | 1.6 | .83 | 18 | 49 | 33 | 1.15 | 34.43 | |
| 35.71 | 79 | 4.6 | .78 | 17 | 57 | 26 | 1.23 | 36.74 | |

| Subject Date Weight | Period | End of Period | Carbon-dioxid, Gm. | Oxygen, Gm. | R. Q. | Water, Gm. | Urine N per Hour, Gm. | Indirect Calo-rimetry, Cal. | Heat Elimi-nated, Cal. | Direct Calo-rimetry (Rectal Temp.) Cal. | Rectal Temp. C. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Morris S. ..... Jan. 27, '14 57.50 kg. | Prelim. | 11:45 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 37.06 |
| | 1 | 12:45 | 19.39 | 17.28 | .82 | 21.44 | 0.365 | 57.63 | 69.67 | 56.44 | 36.79 |
| | 2 | 1:45 | 22.28 | 19.73 | .82 | 21.96 | 0.365 | 65.98 | 71.20 | 73.22 | 36.90 |
| | 3 | 2:45 | 22.21 | 19.73 | .82 | 22.74 | 0.365 | 65.94 | 70.02 | 72.00 | 36.97 |
| Morris S. ..... Dec. 17, '14 61.21 kg. | Prelim. | 11:27 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 36.89 |
| | 1 | 12:27 | 21.46 | 19.30 | .81 | 25.58 | 0.381 | 64.27 | 70.65 | 64.61 | 36.70 |
| | 2 | 1:27 | 23.25 | 21.17 | .80 | 27.85 | 0.381 | 70.42 | 72.99 | 70.69 | 36.79 |
| | 3 | 2:27 | 23.02 | 20.52 | .82 | 27.74 | 0.381 | 68.53 | 72.30 | 68.84 | 36.81 |
| Morris S. ..... Dec. 18, '14 62.81 kg. | Prelim. | 11:00 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 37.02 |
| | 1 | 12:00 | 27.56 | 22.40 | .90 | 31.97 | 0.409 | 76.31 | 77.07 | 71.53 | 36.92 |
| | 2 | 1:00 | 29.29 | 24.39 | .87 | 34.09 | 1.101 | 81.43 | 84.04 | 82.67 | 36.94 |
| | 3 | 2:00 | 23.14 | 19.14 | .88 | 29.33 | 1.101 | 63.50 | 76.85 | 73.79 | 36.89 |
| | 4 | 3:00 | 25.29 | 21.01 | .88 | 31.79 | 1.101 | 69.82 | 78.61 | 74.47 | 36.85 |
| Charles F. .... Nov. 10, '13 57.73 kg. | Prelim. | 11:10 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 38.94 |
| | 1 | 12:10 | 26.83 | 24.23 | .81 | 26.28 | 0.514 | 80.56 | 66.11 | 79.70 | 39.21 |
| | 2 | 1:10 | 27.37 | 25.08 | .79 | 28.78 | 0.514 | 83.17 | 71.87 | 73.83 | 39.26 |
| | 3 | 2:10 | 27.91 | 25.99 | .78 | 43.30 | 0.514 | 85.95 | 88.09 | 77.90 | 39.05 |
| Charles F. .... Nov. 11, '13 58.22 kg. | Prelim. | 11:20 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 38.82 |
| | 1 | 12:20 | 28.97 | 24.58 | .86 | 25.84 | 0.930 | 82.03 | 67.32 | 78.05 | 39.05 |
| | 2 | 1:20 | 30.21 | 26.74 | .82 | 31.12 | 0.930 | 88.58 | 77.70 | 86.96 | 39.25 |
| | 3 | 2:20 | 31.40 | 27.66 | .83 | 31.13 | 0.930 | 91.78 | 82.04 | 99.99 | 39.63 |
| Charles F. .... Nov. 14, '13 57.94 kg. | Prelim. | 11:10 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 39.62 |
| | 1 | 12.10 | 32.69 | 26.60 | .89 | 32.29 | 0.813 | 89.98 | 83.73 | 83.31 | 39.62 |
| | 2 | 1:10 | 31.92 | 25.64 | .91 | 32.26 | 0.813 | 87.23 | 81.28 | 68.87 | 39.37 |
| | 3 | 2:10 | 32.24 | 26.33 | .89 | 32.95 | 0.813 | 88.98 | 89.47 | 91.35 | 39.49 |
| Charles F. .... Nov. 15, '13 57.03 kg. | Prelim. | 11:16 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 39.77 |
| | 1 | 12:16 | 28.26 | 26.44 | .78 | 28.84 | 0.657 | 87.09 | 75.09 | 82.25 | 39.93 |
| | 2 | 1:16 | 28.23 | 26.08 | .79 | 32.35 | 0.657 | 86.12 | 86.12 | 74.34 | 39.88 |
| Charles F. .... Nov. 29, '13 50.36 kg. | Prelim. | 11:26 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 36.71 |
| | 1 | 12:26 | 21.39 | 18.31 | .85 | 29.25 | 0.483 | 61.69 | 61.79 | 59.74 | 36.67 |
| | 2 | 1:26 | 22.05 | 20.15 | .80 | 28.24 | 0.483 | 67.01 | 63.78 | 75.00 | 37.00 |
| | 3 | 2:26 | 21.99 | 19.44 | .82 | 27.10 | 0.483 | 65.08 | 63.75 | 72.92 | 37.25 |
| Charles F. .... Dec. 8, '13 50.99 kg. | Prelim. | 11:10 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 36.90 |
| | 1 | 12:10 | 25.97 | 19.63 | .96 | 21.83 | 0.817 | 66.98 | 62.72 | 52.64 | 36.67 |
| | 2 | 1:10 | 26.73 | 21.61 | .90 | 25.30 | 0.817 | 72.92 | 70.29 | 75.47 | 36.85 |
| | 3 | 2:10 | 25.97 | 21.12 | .90 | 29.04 | 0.817 | 71.13 | 74.23 | 76.85 | 36.95 |
| Charles F. .... Dec. 9, '13 50.38 kg. | Prelim. | 11:06 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 36.78 |
| | 1 | 12:06 | 22.60 | 18.05 | .91 | 19.36 | 0.380 | 61.66 | 58.80 | 55.10 | 36.70 |
| | 2 | 1:06 | 22.10 | 17.29 | .93 | 22.22 | 0.380 | 59.30 | 64.40 | 69.90 | 36.87 |
| | 3 | 2:06 | 21.98 | 17.63 | .91 | 22.36 | 0.380 | 60.15 | 61.83 | 61.55 | 36.88 |
| Charles F. .... Dec. 10, '13 51.09 kg. | Prelim. | 11:10 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 36.89 |
| | 1 | 12:10 | 26.98 | 20.24 | .97 | 22.40 | 0.362 | 70.28 | 62.46 | 58.29 | 36.80 |
| | 2 | 1:10 | 27.70 | 19.45 | 1.04 | 24.37 | 0.362 | 68.24 | 68.32 | 64.48 | 36.76 |
| | 3 | 2:10 | 25.68 | 18.90 | .99 | 28.76 | 0.362 | 65.28 | 72.63 | 60.44 | 36.50 |

—IN TYPHOID FEVER—(*Continued*)

| Surface Temp., C. | Average Pulse | Work Adder., Cm. | Non-Protein, R. Q. | Per Cent. Calories from | | | Calories Per Hour | | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Protein | Fat | Carbohyd. | Per Kg. | Per Sq. M. | |
| 35.61 | | | | | | | | | |
| 35.11 | 60 | 0.5 | .82 | 17 | 51 | 32 | 1.00 | 31.29 | Basal. |
| 35.15 | 71 | 5.6 | .82 | 15 | 51 | 34 | 1.15 | 35.82 | |
| 35.37 | 68 | 5.2 | .82 | 15 | 52 | 33 | 1.15 | 35.80 | |
| ..... | 62 | 4.0 | .81 | 16 | 55 | 29 | 1.05 | 33.61 | Basal. |
| ..... | 65 | 6.0 | .80 | 14 | 58 | 28 | 1.15 | 36.83 | |
| ..... | 62 | 5.0 | .82 | 15 | 52 | 33 | 1.12 | 35.03 | |
| ..... | .. | 5.0 | .91 | 14 | 21 | 65 | 1.22 | 39.23 | At 8:40-9:40 a. m., protein meal; 9.6 gm. N. |
| ..... | 74 | 6.0 | .92 | 36 | 17 | 47 | 1.30 | 41.87 | |
| ..... | 70 | 6.0 | .95 | 46 | 9 | 45 | 1.01 | 32.65 | |
| ..... | 62 | 6.0 | .93 | 42 | 14 | 44 | 1.11 | 35.90 | |
| ..... | 76 | 3.5 | .81 | 17 | 55 | 28 | 1.40 | 43.81 | Basal. |
| ... | 76 | 2.0 | .79 | 16 | 60 | 24 | 1.44 | 45.23 | |
| ..... | 82 | 9.0 | .78 | 16 | 64 | 20 | 1.49 | 46.74 | |
| 37.69 | | | | | | | | | |
| 38.24 | 77 | 3.5 | .88 | 30 | 28 | 42 | 1.41 | 44.34 | 9:10-10:10, protein meal; Nitrogen 6.6 gm. |
| 38.25 | 86 | 13.0 | .82 | 28 | 42 | 30 | 1.52 | 47.88 | |
| 38.34 | 84 | 4.0 | .83 | 27 | 41 | 32 | 1.57 | 49.61 | |
| 38.79 | | | | | | | | | |
| 38.90 | 97 | 15.0 | .96 | 24 | 19 | 57 | 1.56 | 48.80 | At 10:21 a. m., 115 gm commercial glucose. |
| 38.68 | 98 | 8.2 | .94 | 25 | 15 | 60 | 1.52 | 47.31 | |
| 38.79 | 96 | 25.0 | .92 | 24 | 21 | 55 | 1.55 | 48.25 | |
| 38.92 | | | | | | | | | |
| 39.10 | 90 | 17.0 | .77 | 20 | 63 | 17 | 1.53 | 47.75 | Basal. |
| 39.04 | 88 | 15.5 | .78 | 20 | 59 | 21 | 1.51 | 47.22 | |
| ..... | 80 | 13.2 | .86 | 21 | 37 | 42 | 1.23 | 36.81 | Basal. |
| ..... | 86(?) | 16.5 | .79 | 20 | 56 | 24 | 1.33 | 39.98 | |
| ..... | 84 | 18.8 | .83 | 20 | 47 | 33 | 1.30 | 38.83 | |
| 36.24 | | | | | | | | | |
| 36.54 | 74 | 26.6 | 1.05 | 32 | .. | 68 | 1.31 | 39.54 | 9:03-9:45, protein meal: 10.5 gm. N. Work adder too high on account of rapid changes in barometer. |
| 36.16 | 72 | 20.3 | .94 | 30 | 13 | 57 | 1.43 | 43.05 | |
| 36.37 | 84(92) | 15.0 | .94 | 30 | 15 | 55 | 1.40 | 41.99 | |
| .. .. | 75 | 22.3 | .93 | 16 | 19 | 65 | 1.23 | 36.72 | Basal. |
| ..... | 76 | 23.0 | .96 | 17 | 12 | 71 | 1.18 | 35.32 | |
| ..... | 84 | 9.7 | .93 | 17 | 20 | 63 | 1.20 | 35.83 | |
| ..... | 73 | 10.0 | 1.00 | 14 | .. | 86 | 1.38 | 41.46 | At 10:22, 115 gm. commercial glucose. |
| ..... | 87 | 23.5+2? | 1.08 | 14 | .. | 86 | 1.34 | 40.26 | |
| ..... | 81 | 38.0+2? | 1.02 | 15 | .. | 85 | 1.29 | 38.81 | |

TABLE 5.—Clinical Calorimetry—

| Subject Date Weight | Period | End of Period | Carbon-dioxid, Gm. | Oxygen, Gm. | R. Q. | Water, Gm. | Urine N per Hour, Gm. | Indirect Calorimetry, Cal. | Heat Eliminated, Cal. | Direct Calorimetry (Rectal Temp.) Cal. | Rectal Temp. C. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Charles F. .... Dec. 26, '13 55.87 kg. | Prelim. | 11:12 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 36.84 |
| | 1 | 12:12 | 23.75 | 19.16 | .90 | 26.72 | 0.275 | 65.56 | 75.47 | 75.27 | 36.90 |
| | 2 | 1:12 | 21.98 | 18.86 | .85 | 25.23 | 0.275 | 63.65 | 69.83 | 67.08 | 36.86 |
| | 3 | 2:12 | 22.11 | 20.10 | .80 | 25.14 | 0.275 | 67.03 | 70.63 | 69.23 | 36.85 |
| Charles F. .... Dec. 31, '13 55.98 kg. | Prelim. | 1:40 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 37.08 |
| | 1 | 2:40 | 21.85 | 19.82 | .80 | 22.56 | 0.403 | 65.85 | 66.09 | 59.70 | 36.95 |
| | 2 | 3:40 | 22.81 | 21.14 | .78 | 26.98 | 0.403 | 69.98 | 69.09 | 68.75 | 36.95 |
| Howard F. .... Nov. 7, '13 35.47 kg. | Prelim. | 11:16 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 39.74 |
| | 1 | 12:16 | 22.09 | 20.53 | .78 | 22.79 | ..... | 68.25 | 57.28 | 56.71 | 39.73 |
| | 2 | 1:16 | 21.02 | 19.75 | .77 | 24.24 | ..... | 65.53 | 64.17 | 63.90 | 39.73 |
| | 3 | 2 :16 | 20.86 | ..... | .. | 24.06 | ..... | 65.03 ? | 64.99 | 60.30 | 39.56 |
| Howard F. .... Nov. 12, '13 34.98 kg. | Prelim. | 11:24 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 39.64 |
| | 1 | 12:24 | 22.06 | 19.37 | .83 | 20.58 | 0.612 | 64.40 | 58.89 | 61.38 | 39.74 |
| | 2 | 1:24 | 23.23 | 20.40 | .83 | 23.38 | 0.612 | 67.88 | 63.72 | 65.61 | 39.89 |
| | 3 | 2:24 | 22.55 | 21.27 | .77 | 23.60 | 0.612 | 69.78 | 68.49 | 70.09 | 40.15 |
| Howard F. .... Nov. 13, '13 34.19 kg. | Prelim. | 11:00 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 39.76 |
| | 1 | 12:00 | 19.45 | 17.76 | .80 | 22.80 | 0.436 | 58.81 | 57.80 | 59.64 | 39.84 |
| | 2 | 1:00 | 19.64 | 18.46 | .77 | 22.62 | 0.436 | 60.86 | 58.19 | 57.19 | 39.82 |
| | 3 | 2:00 | 20.20 | 19.24 | .76 | 22.66 | 0.436 | 63.22 | 63.74 | 62.17 | 39.78 |
| Howard F. .... Nov. 20, '13 32.54 kg. | Prelim. | 11:30 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 39.31 |
| | 1 | 12:30 | 18.43 | 17.26 | .78 | 27.43 | 0.354 | 56.96 | 55.72 | 55.87 | 39.33 |
| | 2 | 1:30 | 18.27 | 17.42 | .76 | 27.31 | 0.354 | 57.20 | 56.70 | 58.16 | 39.14 |
| | 3 | 2:30 | 17.96 | 17.42 | .75 | 25.62 | 0.354 | 57.10 | 59.75 | 53.97 | 38.94 |
| Howard F. .... Dec. 1, '13 32.93 kg. | Prelim. | 11:06 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 37.03 |
| | 1 | 12:06 | 19.35 | 14.58 | .97 | 18.80 | 0.292 | 50.50 | 45.34 | 42.26 | 36.93 |
| | 2 | 1:06 | 39.56 | 29.26 | .98 | 37.03 | 0.292 | 101.68 | 46.88 | 97.14 | 36.96 |
| | 3 | 2:06 | | | | | | | 50.17 | | 36.97 |
| Howard F. .... Dec. 2, '13 33.06 kg. | Prelim. | 11:12 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 36.84 |
| | 1 | 12:12 | 15.46 | 12.42 | .91 | 17.57 | 0.234 | 42.40 | 44.03 | 42.30 | 36.79 |
| | 2 | 1:12 | 18.09 | 13.48 | .98 | 18.64 | 0.234 | 46.86 | 50.53 | 52.20 | 36.93 |
| Howard F. .... Dec. 5, '13 34.74 kg. | Prelim. | 11:06 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 37.07 |
| | 1 | 12:06 | 22.13 | 17.28 | .93 | 21.01 | 0.614 | 58.85 | 55.03 | 51.80 | 36.97 |
| | 2 | 1:06 | 24.24 | 17.61 | 1.00 | 21.99 | 0.614 | 60.75 | 61.84 | 64.82 | 37.17 |
| | 3 | 2:06 | 24.72 | 19.43 | .93 | 23.61 | 0.614 | 66.21 | 64.12 | 65.52 | 37.25 |
| Howard F. .... Dec. 6, '13 33.78 kg. | Prelim. | 10:56 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 37.02 |
| | 1 | 11:56 | 18.20 | 13.44 | .96 | 17.44 | 0.267 | 46.71 | 47.88 | 46.67 | 36.99 |
| | 2 | 12:56 | 19.17 | 14.84 | .94 | 18.30 | 0.267 | 51.14 | 51.37 | 51.43 | 37.06 |
| Howard F. .... Dec. 18, '13 37.17 kg. | Prelim. | 11:06 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 37.11 |
| | 1 | 12:06 | 19.11 | 16.10 | .86 | 18.73 | 0.314 | 54.38 | 53.61 | 52.94 | 37.10 |
| | 2 | 1:06 | 21.42 | 18.19 | .86 | 20.94 | 0.314 | 61.42 | 58.80 | 63.36 | 37.29 |
| | 3 | 2:06 | 20.93 | 18.62 | .81 | 23.84 | 0.314 | 62.26 | 65.14 | 63.04 | 37.25 |

—IN TYPHOID FEVER—(*Continued*)

| Surface Temp., C. | Average Pulse | Work Adder., Cm. | Non-Protein, R. Q. | Per Cent. Calories from | | | Calories Per Hour | | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Protein | Fat | Carbohyd. | Per Kg. | Per Sq. M. | |
| 36.02 | | | | | | | | | |
| 36.09 | 76 | 23.2 | .92 | 11 | 26 | 63 | 1.18 | 36.44 | Basal |
| 36.38 | .. | 18.3 | .85 | 11 | 44 | 45 | 1.14 | 35.38 | |
| 35.74 | .. | 10.2 | .80 | 11 | 61 | 28 | 1.20 | 37.26 | |
| 36.90 | | | | | | | | | |
| 35.98 | 78 | 4.0 | .80 | 16 | 57 | 27 | 1.18 | 36.38 | Basal. |
| 36.68 | 81 | .... | .78 | 15 | 64 | 21 | 1.25 | 38.66 | |
| ..... | 100 | 10.0 | .... | .. | .. | .. | 1.91 | 51.35 | Basal. Urine not obtained; $O_2$ lost in third period. |
| ..... | 103 | 6.0 | .... | .. | .. | .. | 1.83 | 49.31 | |
| ..... | 106 | 2.0 | .... | .. | .. | .. | 1.83(?) | 48.93(?) | |
| 39.01 | | | | | | | | | |
| 39.13 | 105 | 2.5 | .84 | 25 | 41 | 34 | 1.84 | 48.90 | 9:10-9:40, protein meal; 6.5 gm. N. Asleep most of first period. |
| 39.30 | 104 | 9.5 | .84 | 24 | 42 | 34 | 1.94 | 51.55 | |
| 39.76 | 105 | 5.5 | .76 | 23 | 63 | 14 | 2.00 | 52.99 | |
| ..... | 108 | 1.0 | .79 | 20 | 56 | 24 | 1.72 | 45.34 | Basal. |
| ..... | 108 | 2.5 | .77 | 19 | 65 | 16 | 1.78 | 46.92 | |
| ..... | 104 | 7.7 | .75 | 18 | 79 | 13 | 1.85 | 48.74 | |
| 39.14 | | | | | | | | | |
| 38.80 | 103 | 9.6 | .77 | 16 | 65 | 19 | 1.75 | 45.41 | Basal. |
| 38.68 | 102 | 9.6 | .75 | 16 | 70 | 14 | 1.76 | 45.66 | |
| 38.88 | 92 | 9.5 | .74 | 16 | 75 | 9 | 1.75 | 45.50 | |
| 37.19 | | | | | | | | | |
| 37.16 | 98 | 2.6 | 1.00 | 15 | 1 | 84 | 1.53 | 39.92 | At 10:19, 115 gm. commercial glucose; second and third periods averaged. |
| 36.63 | 97 | 5.1 | 1.02 | 15 | .. | 85 | 1.55 | 40.19 | |
| 37.21 | 97 | 6.0 | | | | | | | |
| 36.92 | | | | | | | | | |
| 36.83 | 75 | 2.5 | .92 | 15 | 22 | 63 | 1.28 | 33.39 | Basal. Asleep most of first hour. |
| 36.60 | 76 | 15.6 | 1.01 | 13 | .. | 87 | 1.42 | 36.90 | |
| ..... | 91 | 7.0 | .99 | 28 | 3 | 69 | 1.70 | 44.90 | 9.00-10:00, protein meal; 10.2 gm. N. Asleep first period. |
| ..... | 90 | 20.5 | 1.08 | 27 | .. | 73 | 1.75 | 46.24 | |
| ..... | 93 | 6.5(?) | .97 | 25 | 8 | 67 | 1.91 | 50.51 | |
| ..... | 73 | 6.6 | 1.02 | 15 | .. | 85 | 1.38 | 36.31 | Basal. Asleep one-half first period. |
| ..... | 76 | 14.2 | .96 | 14 | 11 | 75 | 1.51 | 39.75 | |
| 36.61 | | | | | | | | | |
| 36.82 | 104 | 5.5 | .87 | 15 | 37 | 48 | 1.46 | 39.66 | Basal. Asleep first period. |
| 37.00 | 112 | 13.0 | .87 | 14 | 40 | 46 | 1.65 | 44.79 | |
| 36.76 | 105 | 17.3 | .82 | 13 | 53 | 34 | 1.68 | 45.40 | |

TABLE 5.—CLINICAL CALORIMETRY—

| Subject Date Weight | Period | End of Period | Carbon-dioxid, Gm. | Oxygen, Gm. | R. Q. | Water, Gm. | Urine N per Hour, Gm. | Indirect Calorimetry, Cal. | Heat Eliminated, Cal. | Direct Calorimetry (Rectal Temp.) Cal. | Rectal Temp. C. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Howard F. .... Dec. 30, '13 39.40 kg. | Prelim. | 1:30 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 37.39 |
| | 1 | 2:30 | 19.66 | 17.18 | .83 | 22.45 | 0.278 | 57.68 | 62.50 | 55.92 | 37.10 |
| | 2 | 3:30 | 20.74 | 18.62 | .81 | 23.93 | 0.278 | 62.21 | 60.31 | 61.45 | 37.17 |
| Karl S. ..... Jan. 5, '14 54.64 kg. | Prelim. | 11:50 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 40.14 |
| | 1 | 12:50 | 30.78 | 29.50 | .76 | 39.97 | 0.720 | 96.73 | 101.70 | 91.12 | 39.92 |
| | 2 | 1:50 | 29.73 | 28.53 | .76 | 42.23 | 0.720 | 93.48 | 104.45 | 93.93 | 39.70 |
| Karl S. ..... Jan. 6, '14 54.52 kg. | Prelim. | 12:30 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 39.53 |
| | 1 | 1:30 | 34.01 | 29.51 | .84 | 26.77 | 0.879 | 96.46 | 87.72 | 112.04 | 40.08 |
| | 2 | 2:30 | 35.13 | 31.49 | .81 | 34.31 | 0.879 | 104.43 | 104.20 | 99.22 | 40.05 |
| | 3 | 3:30 | 35.32 | 31.56 | .81 | 38.70 | 0.879 | 104.75 | 107.68 | 105.06 | 40.02 |
| Karl S. ..... Jan. 16, '14 52.21 kg. | Prelim. | 10:50 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 38.29 |
| | 1 | 11:50 | 26.55 | 25.94 | .74 | 26.51 | 0.786 | 84.44 | ..... | ..... | 38.32 |
| | 2 | 1:02 | 32.40 | 28.88 | .82 | 38.71 | 0.943 | 95.01 | ..... | ..... | 38.22 |
| | 3 | 1:50 | 21.52 | 19.72 | .80 | 22.34 | 0.655 | 64.72 | ..... | ..... | 38.14 |
| Karl S. ..... Jan. 19, '14 51.19 kg. | Prelim. | 10:50 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 36.36 |
| | 1 | 11:50 | 20.70 | 16.34 | .92 | 12.72 | 0.522 | 55.62 | ..... | ..... | 36.54 |
| | 2 | 12:50 | 22.08 | 18.41 | .87 | 28.28 | 0.522 | 62.03 | ..... | ..... | 36.55 |
| | 3 | 1:50 | 22.53 | 19.41 | .84 | 32.55 | 0.522 | 64.96 | ..... | ..... | 36.57 |
| Karl S. ..... Jan. 21, '14 51.29 kg. | Prelim. | 12:30 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 36.72 |
| | 1 | 1:30 | 24.09 | 19.71 | .89 | 32.46 | 0.868 | 66.11 | ..... | ..... | 36.55 |
| | 2 | 2:30 | 23.96 | 19.57 | .89 | 25.79 | 0.868 | 65.65 | ..... | ..... | 36.29 |
| | 3 | 3:30 | 26.95 | 21.45 | .91 | 32.17 | 0.868 | 72.55 | ..... | ..... | 36.46 |
| Karl S. ..... Jan. 22, '14 50.63 kg. | Prelim. | 12:40 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 36.75 |
| | 1 | 1:40 | 18.66 | 15.37 | .88 | 16.87 | 0.423 | 51.92 | ..... | ..... | 36.54 |
| | 2 | 2:40 | 21.01 | 16.98 | .90 | 20.51 | 0.423 | 57.70 | ..... | ..... | 36.40 |
| | 3 | 3:40 | 20.54 | 17.06 | .88 | 22.17 | 0.423 | 57.62 | ..... | ..... | 36.48 |
| Karl S. ..... Feb. 6, '14 52.30 kg. | Prelim. | 11:05 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 37.15 |
| | 1 | 12:05 | 23.16 | 20.28 | .83 | 23.98 | 0.324 | 68.07 | 67.22 | 58.11 | 36.95 |
| | 2 | 1:05 | 21.97 | 18.82 | .85 | 22.85 | 0.324 | 63.43 | 67.46 | 56.97 | 36.72 |
| | 3 | 2:05 | 25.49 | 24.36 | .76 | 27.16 | 0.324 | 80.44 | 74.45 | 80.28 | 36.86 |
| Karl S. ..... Feb. 7, '14 54.45 kg. | Prelim. | 10:46 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 37.35 |
| | 1 | 11:46 | 27.92 | 22.71 | .89 | 32.41 | 0.581 | 77.05 | 77.13 | 60.51 | 36.99 |
| | 2 | 12:46 | 27.33 | 21.87 | .91 | 29.12 | 0.581 | 74.43 | 79.33 | 74.48 | 36.89 |
| | 3 | 1:46 | 26.23 | 21.16 | .90 | 32.41 | 0.581 | 71.85 | 79.75 | 76.71 | 36.83 |
| Thomas B. .... Oct. 15, '13 73.62 kg. | Prelim. | 10:48 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 36.79 |
| | 1 | 11:48 | 24.87 | 22.60 | .80 | 23.50 | 0.506 | 75.00 | 48.97 | 70.72 | 37.13 |
| | 2 | 12:48 | 27.05 | 22.82 | .86 | 24.88 | 0.506 | 76.95 | 56.97 | 72.61 | 37.38 |
| | 3 | 1:48 | 26.46 | 24.69 | .78 | 26.[illegible] | 0.506 | 81.57 | 63.67 | 74.67 | 37.58 |
| | 4 | 2:48 | 28.39 | 24.58 | .84 | 28.78 | 0.506 | 82.49 | 67.66 | 79.68 | 37.78 |
| Thomas B. .... Oct. 21, '13 72.56 kg. | Prelim. | 10:24 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 36.60 |
| | 1 | 11:24 | 22.98 | 20.14 | .88 | 24.71 | 0.407 | 67.43 | ..... | 52.61 | 36.71 |
| | 2 | 12:24 | 24.90 | 19.11 | .95 | 29.05 | 0.407 | 65.88 | 65.03 | 63.75 | 36.71 |
| | 3 | 1:24 | 26.13 | 20.21 | .94 | 30.15 | 0.407 | 69.58 | 68.06 | 69.32 | 36.64 |

—IN TYPHOID FEVER—(*Continued*)

| Surface Temp., C. | Average Pulse | Work Adder., Cm. | Non-Protein, R. Q. | Per Cent. Calories from | | | Calories Per Hour | | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Protein | Fat | Carbohyd. | Per Kg. | Per Sq. M. | |
| 36.57 | | | | | | | | | |
| 36.44 | 109 | 6.5 | .84 | 13 | 48 | 39 | 1.47 | 40.49 | Basal. Asleep greater part of both periods. |
| 36.60 | 107 | 8.5 | .81 | 12 | 57 | 31 | 1.58 | 43.67 | |
| 39.24 | | | | | | | | | |
| 38.97 | 114 | 8.4 | .75 | 20 | 69 | 11 | 1.77 | 54.93 | Basal. |
| 38.67 | 109 | 6.7 | .75 | 20 | 69 | 11 | 1.71 | 53.08 | |
| 38.60 | | | | | | | | | |
| 39.61 | 107 | 8.8 | .85 | 24 | 39 | 37 | 1.80 | 55.62 | 9:45-10:12, protein meal; 10.5 gm. N. |
| 39.39 | 99(?) | 14.6 | .81 | 22 | 50 | 28 | 1.92 | 59.00 | |
| 39.27 | 119 | 13.0 | .82 | 22 | 49 | 29 | 1.92 | 59.18 | |
| ..... | 92 | 12.2 | .72 | 25 | 70 | 5 | 1.62 | 49.09 | Basal. Water ther. broken. Second period 72 min. long on account movement. |
| ..... | 96 | 21.0+3? | .82 | 26 | 44 | 30 | 1.53 | 46.03 | |
| .... | 96 | 11.0 | .77 | 26 | 57 | 17 | 1.55 | 45.15 | |
| ..... | 76 | 10.6 | .96 | 25 | 9 | 66 | 1.09 | 32.74 | Basal. |
| ..... | 76 | 14.8+4 | .89 | 22 | 28 | 50 | 1.21 | 36.51 | |
| ..... | 78 | 16.8 | .86 | 21 | 39 | 40 | 1.27 | 38.25 | |
| ..... | 73 | 9.8 | .94 | 34 | 14 | 52 | 1.29 | 38.89 | 9:35-11:36, protein meal; 10.0 gm. N. |
| ..... | 69 | 5.7 | .94 | 35 | 13 | 52 | 1.28 | 38.62 | |
| ..... | 74 | 17.0 | .97 | 31 | 7 | 62 | 1.42 | 42.68 | |
| ..... | 59 | 4.0 | .91 | 22 | 25 | 53 | 1.03 | 30.81 | Basal. Asleep first period. |
| ..... | 57 | 11.7 | .93 | 20 | 20 | 60 | 1.14 | 34.24 | |
| ..... | 68 | 9.2 | .90 | 20 | 29 | 51 | 1.14 | 34.20 | |
| 36.20 | | | | | | | | | |
| 36.52 | 81 | 15.5 | .84 | 13 | 49 | 38 | 1.28 | 39.03 | Basal. Asleep about 50 min. in first period and 50 min. in second. |
| 35.86 | 79 | 9.4 | .86 | 14 | 42 | 44 | 1.19 | 36.37 | |
| 35.97 | 82 | 25.2 | .76 | 11 | 74 | 15 | 1.51 | 46.12 | |
| 36.40 | | | | | | | | | |
| 36.58 | 94 | 12.4 | .92 | 20 | 22 | 58 | 1.41 | 43.56 | 7:30-7:40, 44.3 gm. protein; 9:35-9:37, 15.6 gm. protein; total, 9.6 gm. N. Asleep most of the time. |
| 35.97 | 90 | 7.2 | .94 | 21 | 16 | 63 | 1.37 | 42.07 | |
| 36.24 | 86 | 11.0 | .93 | 21 | 19 | 60 | 1.32 | 40.62 | |
| ..... | 81 | 8.0 | .80 | 13 | 56 | 26 | 1.02 | 34.67 | Basal. |
| ..... | 85 | 14.0 | .88 | 17 | 35 | 48 | 1.05 | 35.58 | |
| ..... | 84 | 7.6 | .77 | 16 | 65 | 19 | 1.11 | 37.71 | |
| ..... | 91 | 21.0 | .85 | 16 | 43 | 41 | 1.12 | 38.14 | |
| ..... | 73(?) | 12.0 | .84 | 16 | 47 | 37 | 0.93 | 31.48 | Basal. |
| ..... | 78 | 19.0 | .98 | 16 | 6 | 78 | 0.91 | 30.76 | |
| ..... | 84 | .... | .97 | 16 | 9 | 75 | 0.96 | 32.48 | |

TABLE 5.—CLINICAL CALORIMETRY

| Subject Date Weight | Period | End of Period | Carbon-dioxid, Gm. | Oxygen, Gm. | R. Q. | Water, Gm. | Urine N per Hour, Gm. | Indirect Calo-rimetry, Cal. | Heat Elimi-nated, Cal. | Direct Calo-rimetry (Rectal Temp.) Cal. | Rectal Temp. C. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Richard T. .... Oct. 18, '13 36.49 kg. | Prelim. | 9:48 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 38.13 |
| | 1 | 10:48 | 20.39 | 18.59 | .80 | 30.29 | 0.403 | 61.65 | 43.77 | 57.62 | 38.99 |
| | 2 | 11:48 | 21.06 | 18.24 | .84 | 21.24 | 0.403 | 61.12 | 42.57 | 66.86 | 39.50 |
| | 3 | 12:48 | 20.49 | 18.68 | .80 | 25.61 | 0.403 | 61.95 ? | 45.94 | 52.35 | 39.74 |
| Richard T. .... Oct. 20, '13 35.37 kg. | Prelim. | 10:16 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 37.68 |
| | 1 | 11:16 | 18.98 | 15.18 | .91 | 31.21 | 0.499 | 51.48 | 42.37 | 58.44 | 38.24 |
| | 2 | 12:16 | 21.25 | 18.39 | .84 | 31.41 | 0.499 | 61.49 | 47.46 | 58.51 | 38.63 |
| | 3 | 1:16 | 19.90 | 17.96 | .81 | 29.74 | 0.499 | 59.49 | 48.42 | 46.90 | 38.64 |
| Anton K. ..... Oct. 16, '13 50.55 kg. | Prelim. | 11:16 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 36.99 |
| | 1 | 12:16 | 22.48 | 18.64 | .88 | 30.88 | 0.479 | 62.98 | 61.00 | 61.00 | 36.99 |
| | 2 | 1:16 | 21.65 | 19.08 | .83 | 33.40 | 0.479 | 63.64 | 66.45 | 72.34 | 37.14 |
| | 3 | 2:16 | 23.57 | 19.73 | .87 | 30.29 | 0.479 | 66.57 | 64.84 | 68.64 | 37.24 |
| Rose G. ..... Nov. 22, '13 30.11 kg. | Prelim. | 11:04 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 37.04 |
| | 1 | 12:04 | 17.77 | 15.73 | .82 | 28.24 | ..... | 52.81 | 51.24 | 53.76 | 37.15 |
| | 2 | 12:34 | 9.28 | 7.28 | .93 | 17.44 | ..... | 24.98 | 28.36 | 24.99 | 37.02 |
| Edw. B. ..... Oct. 23, '14 55.76 kg. | Prelim. | 12:07 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 38.07 |
| | 1 | 1:07 | 25.02 | 22.61 | .81 | 30.22 | 0.187 | 75.66 | 62.23 | 70.20 | 38.25 |
| | 2 | 2:07 | 25.51 | 23.48 | .79 | 28.78 | 0.187 | 78.30 | 64.70 | 81.43 | 38.62 |
| | 3 | 3:07 | 27.24 | 25.59 | .77 | 29.84 | 0.187 | 85.03 | 70.05 | 71.67 | 38.88 |
| Edw. B. ..... Oct. 26, '14 56.10 kg. | Prelim. | 11:24 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 37.54 |
| | 1 | 12:24 | 23.13 | 19.58 | .86 | 31.21 | 0.264 | 66.36 | 61.58 | 66.23 | 37.65 |
| | 2 | 1:24 | 24.87 | 23.79 | .76 | 29.49 | 0.264 | 78.72 | 60.08 | 67.98 | 37.83 |
| | 3 | 2:24 | 25.18 | 22.90 | .80 | 30.36 | 0.264 | 76.47 | 65.45 | 73.34 | 38.01 |
| | 4 | 3:24 | 26.12 | 23.21 | .82 | 31.13 | 0.264 | 77.87 | 70.55 | 84.46 | 38.32 |
| Edw. B. ..... Oct. 27, '14 56.84 kg. | Prelim. | 11:20 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 37.40 |
| | 1 | 12:20 | 24.80 | 21.91 | .82 | 30.89 | 0.552 | 73.08 | 60.09 | 59.69 | 37.46 |
| | 2 | 1:20 | 23.76 | 22.13 | .78 | 29.26 | 0.552 | 73.01 | 61.33 | 70.63 | 37.68 |
| | 3 | 2:20 | 23.24 | 22.30 | .76 | 28.83 | 0.552 | 73.13 | 63.78 | 73.06 | 37.91 |
| Edw. B. ..... Nov. 4, '14 58.72 kg. | Prelim. | 11:15 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 37.16 |
| | 1 | 12:15 | 24.00 | 19.79 | .88 | 31.79 | 0.337 | 67.32 | 64.06 | 64.69 | 37.18 |
| | 2 | 1:15 | 25.03 | 21.77 | .84 | 31.06 | 0.337 | 73.17 | 65.16 | 69.21 | 37.27 |
| | 3 | 2:15 | 24.89 | 21.98 | .82 | 31.62 | 0.337 | 73.72 | 70.13 | 74.19 | 37.36 |
| Edw. B. ..... Nov. 6, '14 59.78 kg. | Prelim. | 11:15 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 38.84 |
| | 1 | 12:15 | 26.21 | 23.22 | .82 | 27.40 | 0.336 | 77.76 | 62.39 | 81.16 | 39.28 |
| | 2 | 1:15 | 26.65 | 23.45 | .83 | 28.17 | 0.336 | 78.07 | 64.20 | 69.44 | 39.41 |
| | 3 | 2:15 | 26.61 | 23.39 | .82 | 30.30 | 0.336 | 78.33 | 68.49 | 72.75 | 39.52 |
| Edw. B. ..... Nov. 10, '14 56.87 kg. | Prelim. | 11:15 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 40.22 |
| | 1 | 12:15 | 30.59 | 30.14 | .74 | 35.32 | 0.525 | 98.74 | 88.56 | 86.50 | 40.33 |
| | 2 | 1:15 | 29.52 | 27.49 | .78 | 36.30 | 0.525 | 90.99 | 87.53 | 91.26 | 40.43 |
| | 3 | 2:15 | 30.25 | ..... | .. | 39.54 | 0.525 | ..... | 94.67 | 86.34 | 40.26 |
| John K. ..... Dec. 15, '14 68.81 kg. | Prelim | 11:56 | ..... | ..... | .. | ..... | ..... | ..... | ..... | ..... | 39.00 |
| | 1 | 12:56 | 30.97 | 28.17 | .80 | 34.02 | 1.258 | 92.29 | 86.30 | 94.23 | 39.26 |
| | 2 | 1:56 | 30.59 | 30.08 | .74 | 39.95 | 1.258 | 97.14 | 91.58 | 87.82 | 39.22 |

—IN TYPHOID FEVER—(*Continued*)

| Surface Temp., C. | Average Pulse | Work Adder., Cm. | Non-Protein, R. Q. | Per Cent. Calories from | | | Calories Per Hour | | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Protein | Fat | Carbohyd. | Per Kg. | Per Sq. M. | |
| ..... | 81 | 31.4 | .80 | 17 | 57 | 26 | 1.69 | 45.50 | Basal. Somewhat restless. |
| ..... | 98 | 16.2 | .85 | 17 | 43 | 40 | 1.68 | 45.11 | |
| ..... | .. | 18.5 | .80 | 17 | 57 | 26 | 1.70 | 45.72 | |
| ..... | 82 | 22.0 | .95 | 26 | 13 | 61 | 1.45 | 38.79 | Basal. |
| .... | 102 | 30.0 | .85 | 22 | 40 | 38 | 1.74 | 46.34 | |
| ..... | 95 | 17.0 | .81 | 22 | 50 | 28 | 1.68 | 44.83 | |
| ..... | 76 | 21.0 | .90 | 20 | 28 | 52 | 1.25 | 37.42 | Basal. |
| ..... | 81 | 19.0 | .83 | 20 | 46 | 34 | 1.26 | 37.81 | |
| ..... | 80 | 13.0 | .89 | 19 | 22 | 49 | 1.32 | 39.55 | |
| 35.75 | | | | | | | | | |
| 36.05 | 79 | 16.0 | .... | .. | .. | .. | 1.75 | 44.32 | Basal. Restless. Second period ½ hr. long because patient voided in bed. |
| 36.10 | 76 | 9.0 | .... | .. | .. | .. | 1.66 | 41.93 | |
| ..... | 118 | 12.0 | .81 | 7 | 49 | 44 | 1.36 | 42.10 | Basal. |
| ..... | 115 | 17.0 | .79 | 6 | 67 | 27 | 1.40 | 43.57 | |
| ..... | 116 | 24.0 | .77 | 6 | 73 | 21 | 1.53 | 47.32 | |
| ..... | 105 | 11.0 | .87 | 11 | 39 | 50 | 1.18 | 36.78 | 10:25 a. m., 79 gm. olive oil = 750 calories. |
| ..... | 117 | 10.0 | .76 | 9 | 74 | 17 | 1.40 | 43.64 | |
| ..... | 126 | 10.0 | .80 | 9 | 62 | 29 | 1.36 | 42.39 | |
| ..... | 123 | 15.0 | .82 | 9 | 56 | 35 | 1.39 | 43.17 | |
| ..... | 106 | 14.0 | .83 | 19 | 47 | 34 | 1.29 | 40.16 | Basal. |
| ..... | 109 | 22.0 | .78 | 19 | 61 | 20 | 1.29 | 40.12 | |
| ..... | 107 | 14.0 | .75 | 19 | 69 | 12 | 1.29 | 40.18 | |
| ..... | 102 | 10.6 | .90 | 13 | 30 | 57 | 1.15 | 36.19 | Basal. |
| ..... | 104 | 14.0 | .84 | 12 | 48 | 40 | 1.25 | 39.34 | |
| ..... | 105 | 25.0 | .83 | 12 | 51 | 37 | 1.26 | 39.64 | |
| ..... | ... | 31.0 | .82 | 11 | 54 | 35 | 1.30 | 41.32 | Basal. Rising temp. |
| ..... | 124 | 5.0 | .83 | 11 | 51 | 38 | 1.31 | 41.48 | |
| ..... | 124 | 12.0 | .82 | 11 | 54 | 35 | 1.31 | 41.62 | |
| ..... | 141 | 24.0 | .73 | 14 | 79 | 7 | 1.74 | 54.31 | Basal. Very high temp. Mildly delirious. |
| ..... | 142 | 30.5 | .78 | 15 | 64 | 21 | 1.60 | 50.05 | |
| ..... | 140 | 16.0++ | | | | | | | |
| ..... | 62 | 16.0 | .80 | 26 | 43 | 21 | 1.45 | 46.94 | Basal. |
| ..... | 63 | 14.0 | .70 | 34 | 66 | 0 | 1.52 | 49.41 | |

TABLE 6.—Clinical Data

Charles F.

| Date, 1913 | Food | | | Food N., Gm. | Urine N., Gm. | Excreta N., Gm. | Nitrogen Bal., Gm. | Body Wt., Kg. | Urine Vol., C.c. |
|---|---|---|---|---|---|---|---|---|---|
| | Total Calories | Carbohydrate, Gm. | Fat, Gm. | | | | | | |
| Nov. 6.... | 1,465 | 88.0 | 96.0 | 8.3 | 14.68 | 15.51† | —7.21 | 58.56 | 1,270 |
| Nov. 7.... | ..... | ..... | ..... | .... | 15.52 | ..... | ..... | ..... | 1,600 |
| Nov. 8.... | 1,855 | 116.0 | 123.0 | 9.1 | 21.10 | 22.01 | —12.91 | ..... | 2,300 |
| Nov. 9.... | 2,065 | 130.0 | 135.0 | 10.8 | 20.45 | 21.53 | —10.73 | ..... | 1,870 |
| Nov. 10.... | 1,088 | 80.0 | 69.0 | 4.4 | 16.22 | 16.66 | —12.26 | 57.76 | 1,205 |
| Nov. 11.... | 2,027 | 214.0 | 87.0 | 13.2 | 22.28 | 23.60 | —10.40 | 58.25 | 1,740 |
| Nov. 12.... | 2,610 | 231.0 | 144.0 | 9.8 | 18.92 | 19.90 | —10.10 | ..... | 2,110 |
| Nov. 13.... | 2,255 | 218.0 | 118.0 | 10.2 | 17.37 | 18.39 | —8.19 | 57.88 | 1,900 |
| Nov. 14.... | 1,290 | 203.0 | 50.0 | 3.8 | 16.03 | 16.41 | —12.61 | 57.60 | 1,235 |
| Nov. 15.... | 1,286 | 148.0 | 60.0 | 4.6 | 18.54 | 19.00 | —14.40 | 56.86 | 1,270 |
| Nov. 16.... | 1,440 | 151.0 | 72.0 | 5.7 | 18.89 | 19.46 | —13.76 | ..... | 1,960 |
| Nov. 17.... | 1,492 | 128.0 | 83.0 | 7.6 | 17.82 | 18.58 | —10.98 | ..... | 2,110 |
| Nov. 18.... | 1,749 | 133.0 | 107.0 | 8.1 | 20.34 | 21.15 | —13.05 | 56.01 | 1,470 |
| Nov. 19.... | 1,019 | 63.0 | 68.0 | 5.2 | 22.13 | 22.65 | —17.45 | ..... | 1,360 |
| Nov. 20.... | 1,323 | 93.0 | 76.0 | 8.7 | 22.41 | 23.28 | —14.58 | ..... | 1,380 |
| Nov. 21.... | 1,426 | 74.0 | 98.0 | 8.1 | 22.81 | 23.62 | —15.52 | ..... | 1,380 |
| Nov. 22.... | 1,970 | 122.0 | 128.0 | 10.2 | 20.50 | 21.59 | —10.69 | ..... | 1,900 |
| Nov. 23.... | 1,787 | 112.0 | 115.0 | 10.6 | 18.16 | 19.22 | —8.62 | ..... | 1,680 |
| Nov. 24.... | 1,696 | 117.0 | 101.0 | 10.4 | 18.16 | 19.20 | —8.80 | 52.02 | 1,580 |
| Nov. 25.... | 2,443 | 159.0 | 155.0 | 13.8 | 18.95 | 20.33 | —6.53 | ..... | 1,910 |
| Nov. 26.... | 2,595 | 174.0 | 160.0 | 15.4 | 18.92 | 20.46 | —5.06 | 51.48 | 20.50 |
| Nov. 27.... | 2,345 | 173.0 | 142.0 | 12.3 | 18.41 | 19.64 | —7.34 | ..... | 1,920 |
| Nov. 28.... | 2,646 | 223.0 | 150.0 | 13.1 | 16.65 | 17.96 | —4.86 | 50.98 | 2,120 |
| Nov. 29.... | * 1,908 | 129.0 | 126.0 | 7.8 | 13.91 | 14.69 | —6.89 | 50.29 | 1,150 |
| Nov. 30.... | 2,825 | 236.0 | 158.0 | 15.2 | 15.58 | 17.10 | —1.90 | ..... | 1,700 |
| Dec. 1.... | 3,491 | 314.0 | 196.0 | 14.9 | 14.12 | 15.61 | —0.71 | 50.50 | 1,760 |
| Dec. 2.... | 3,126 | 310.0 | 160.0 | 14.3 | 12.33 | 13.76 | +0.54 | ..... | 1,480+ |
| Dec. 3.... | 2,595 | 279.0 | 118.0 | 13.7 | 11.99 | 13.36 | +0.34 | 50.79 | 1,600 |
| Dec. 4.... | 3,408 | 382.0 | 150.0 | 17.4 | 12.69 | 14.43 | +2.96 | ..... | 1,480 |
| Dec. 5.... | 2,083 | 302.0 | 87.0 | 15.0 | 12.05 | 13.55 | +1.45 | ..... | 1,580 |
| Dec. 6.... | 2,827 | 390.0 | 88.0 | 15.9 | 12.67 | 14.26 | +1.64 | 49.83 | 1.401 |
| Dec. 7.... | 3,223 | 446.0 | 106.0 | 16.0 | 12.72 | 14.32 | +1.68 | 49.83 | 1,740 |
| Dec. 8.... | 2,182 | 346.0 | 94.0 | 20.0 | 16.27 | 18.27 | +1.73 | 51.02 | 1,220 |
| Dec. 9.... | 2,426 | 308.0 | 91.0 | 12.5 | 12.04 | 13.29 | —0.79 | 50.41 | 695 |
| Dec. 10.... | 2.905 | 432.0 | 88.0 | 12.3 | 10.01 | 11.24 | +1.06 | 50.80 | 1,100 |
| Dec. 11.... | 3,485 | 503.0 | 107.0 | 16.7 | 9.47 | 11.14 | +5.56 | ..... | 1,640 |
| Dec. 12.... | 3,768 | 556.0 | 115.0 | 16.3 | 9.92 | 11.55 | +4.75 | ..... | 1,500 |
| Dec. 13.... | 4,025 | 619.0 | 129.0 | 18.2 | 10.48 | 12.30 | +5.90 | 53.16 | 1,880 |
| Dec. 14.... | 3,600 | 549.0 | 105.0 | 16.8 | 10.59 | 12.27 | +4.53 | ..... | 1,470 |

* Estimate heat production 1,725.

TABLE 6.—Clinical Data—(*Continued*)

Charles F.—(*Continued*)

| Date, 1913 | Food | | | Food N., Gm. | Urine N., Gm. | Excretn N., Gm. | Nitrogen Bal., Gm. | Body Wt., Kg. | Urine Vol., C.c. |
|---|---|---|---|---|---|---|---|---|---|
| | Total Calories | Carbohydrate, Gm. | Fat, Gm. | | | | | | |
| Dec. 15.... | 4.032 | 585.0 | 124.0 | 18.8 | 9.93 | 11.81 | +6.99 | 52.81 | 1,330+ |
| Dec. 16.... | 3.921 | 573.0 | 118.0 | 18.6 | 11.67 | 13.53 | +5.07 | 54.05 | 1,280 |
| Dec. 17.... | 3,539 | 510.0 | 109.0 | 16.9 | 11.15 | 12.84 | +4.06 | ..... | 1,470 |
| Dec. 18.... | 3,869 | 572.0 | 113.0 | 18.2 | 11.54 | 13.36 | +4.84 | ..... | 1,800 |
| Dec. 19.... | 4,085 | 630.0 | 112.0 | 17.9 | 10.39 | 12.18 | +5.72 | ..... | 1,500 |
| Dec. 20.... | 3,901 | 599.0 | 105.0 | 18.5 | 11.04 | 12.89 | +5.61 | ..... | 1,760 |
| Dec. 21.... | 4.017 | 620.0 | 105.0 | 19.3 | 11.43 | 13.36 | +5.94 | ..... | 1,850 |
| Dec. 22.... | 3,351 | 282.0 | 189.0 | 17.1 | 12.33 | 14.04 | +3.06 | 55.43 | 1,700 |
| Dec. 23.... | 3,722 | 241.0 | 249.0 | 16.4 | 11.46 | 13.10 | +3.30 | ..... | 1,180 |
| Dec. 24.... | 3,739 | 228.0 | 254.0 | 17.5 | 13.14 | 14.89 | +2.61 | ..... | 1,440 |
| Dec. 25.... | ..... | ..... | ..... | .... | 9.28 | ..... | ..... | ..... | 1.500 |
| Dec. 26.... | 2,122 | 153.0 | 137.0 | 12.4 | 9.40 | 10.64 | +1.76 | 55.91 | 1,940 |
| Dec. 27.... | 3,626 | 254.0 | 224.0 | 20.0 | 12.16 | 14.16 | +5.84 | ..... | 1,600 |
| Dec. 28.... | 3,614 | 247.0 | 226.0 | 19.4 | 12.86 | 14.80 | +4.60 | ..... | 1,640 |
| Dec. 29.... | 3,818 | 221.0 | 259.0 | 19.0 | 12.78 | 14.66 | +4.34 | ..... | 1,820 |
| Dec. 30.... | 4,899 | 256.0 | 347.0 | 24.2 | 11.49 | 13.91 | +10.29 | ..... | 1,480 |
| Dec. 31.... | 2,131 | 202.0 | 103.0 | 13.3 | 11.53 | 12.86 | +0.44 | 56.43 | 1,571 |
| 1914 | | | | | | | | | |
| Jan. 1.... | 3,949 | 347.0 | 161.0 | 18.6 | 11.54 | 13.40 | +5.20 | ..... | 1,000 |
| Jan. 2.... | 3,587 | 287.0 | 202.0 | 22.0 | 8.10 | 10.30 | +11.70 | ..... | 860 |

† Excreta nitrogen estimated as urine nitrogen + 10 per cent. of food nitrogen.

TABLE 6.—CLINICAL DATA—(*Continued*)

MORRIS S.

| Date, 1913 | Estimated Heat Production per 24 Hrs. | Food | | | Food N., Gm. | Urine N., Gm. | Feces N., Gm. | Excreta N., Gm. | Nitrogen Bal., Gm. | Body Weight Kg. | Urine Volume, C.c. | Feces Fat |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Total Calories | Carbohydrate, Gm. | Fat, Gm. | | | | | | | | |
| Oct. 23 | ..... | 2,962 | 419.0 | 76.0 | 20.8 | 15.13 | 3.1* | 18.2 | +2.6 | 49.69 | 1,280 | |
| Oct. 24 | 2,376 | 1,259 | 169.0 | 28.0 | 11.8 | 19.56 | 1.7* | 21.3 | −9.5 | 51.50 | 2,350 | |
| Oct. 25 | 2,299 | 2,371 | 364.0 | 36.0 | 21.3 | 13.59 | 3.2* | 16.8 | +4.5 | 51.22 | 1,710 | |
| Oct. 26 | ..... | 4,375 | 471.0 | 101.0 | 19.5 | 20.34 | 2.9 | 23.2 | −3.7 | ..... | 3,000 | |
| Oct. 27 | ..... | 3,194 | 321.0 | 152.0 | 18.2 | 21.60 | 2.7 | 24.3 | −6.1 | 51.26 | 2,170 | |
| Oct. 28 | 2,200 | 2,332 | 242.0 | 116.0 | 10.0 | 17.43 | 1.5 | 18.9 | −8.9 | 51.18 | 1,390 | |
| Oct. 29 | 2,228 | 2,876 | 258.0 | 150.0 | 16.4 | 20.38 | 2.5 | 22.9 | −6.5 | 50.17 | 1,465 | |
| Oct. 30 | ..... | 3,081 | 318.0 | 141.0 | 15.5 | 18.72 | 2.31 | 21.03 | −5.5 | 49.85 | 1,580 | 9.74 |
| Oct. 31 | 2,225 | 2,784 | 224.0 | 149.0 | 18.0 | 22.28 | 2.31 | 24.59 | −6.6 | 50.32 | 1,830 | 9.74 |
| Nov. 1 | ..... | 3,069 | 327.0 | 147.0 | 14.8 | 17.48 | 2.31 | 19.79 | −5.0 | 49.82 | 1,600 | 9.74 |
| Nov. 2 | ..... | 3,039 | 324.0 | 142.0 | 15.2 | 16.76 | 2.31 | 19.07 | −3.9 | ..... | 1,600 | 9.74 |
| Nov. 3 | 2,205 | 3,069 | 324.0 | 142.0 | 15.2 | 17.39 | 2.31 | 19.70 | −4.5 | 48.88 | 1,370 | 9.74 |
| Nov. 4 | ..... | 3,069 | 324.0 | 142.0 | 15.2 | 15.86 | 2.31 | 18.17 | −3.0 | 49.63 | 1,220 | 9.74 |
| Nov. 5 | 2,104 | 3,024 | 324.0 | 139.0 | 15.4 | 15.57 | 2.31 | 17.88 | −2.5 | 48.48 | 1,160 | 9.74 |
| Nov. 6 | ..... | 3,039 | 325.0 | 147.0 | 15.4 | 13.51 | 2.3 | 15.8 | −0.4 | 49.03 | 1,310 | |
| Nov. 7 | ..... | 3,084 | 327.0 | 140.0 | 15.0 | 12.39 | 2.3 | 14.7 | +0.3 | ..... | 1,220 | |
| Nov. 8 | ..... | 3,018 | 319.0 | 142.0 | 15.0 | 11.24 | 2.3 | 13.5 | +1.5 | 48.73 | 1,310 | |
| Nov. 9 | ..... | 3,048 | 321.0 | 144.0 | 15.4 | 11.71 | 2.3 | 14.0 | +1.4 | ..... | 1,240 | |
| Nov. 10 | ..... | 2,969 | 305.0 | 144.0 | 14.9 | 12.05 | 2.2 | 14.3 | +0.6 | ..... | 2,000 | |
| Nov. 11 | ..... | 3,004 | 324.0 | 140.0 | 14.8 | 10.23 | 2.2 | 12.4 | +2.4 | 48.05 | 1,220 | |
| Nov. 12 | ..... | 2,998 | 314.0 | 142.0 | 15.2 | 12.78 | 2.3 | 15.1 | +0.1 | ..... | 1,380 | |
| Nov. 13 | ..... | 2,998 | 314.0 | 142.0 | 15.2 | 11.43 | 2.3 | 13.7 | +1.5 | ..... | 1,480 | |
| Nov. 14 | .... | 3,181 | 331.0 | 142.0 | 15.4 | 10.54 | 2.3 | 12.8 | +2.6 | ..... | 1,390 | |
| Nov. 15 | ..... | 2,994 | 313.0 | 142.0 | 15.2 | 10.42 | 2.3 | 12.7 | +2.5 | ..... | 2,000 | |
| Nov. 16 | ..... | 3,134 | 341.0 | 144.0 | 15.3 | 11.44 | 2.3 | 13.7 | +1.6 | ..... | 1,820 | |
| Nov. 17 | 1,875 | 3,076 | 333.0 | 142.0 | 15.2 | 13.32 | 2.3 | 15.6 | −0.4 | 48.80 | 1,690 | |
| Nov. 18 | 2,062 | 1,987 | 217.0 | 95.0 | 8.0 | 15.19 | 1.2 | 16.4 | −8.4 | 49.06 | 1,440 | |
| Nov. 19 | ..... | 1,355 | 148.0 | 61.0 | 7.7 | 15.47 | 1.2 | 16.7 | −9.0 | ..... | 2,280 | |
| Nov. 20 | ..... | 1,727 | 199.0 | 79.0 | 7.0 | 15.13 | 1.1 | 16.2 | −9.2 | ..... | 1,300 | |
| Nov. 21 | ..... | 1,805 | 171.0 | 95.0 | 8.4 | 14.74 | 1.3 | 16.0 | −7.6 | ..... | 900 | |
| Nov. 22 | ..... | 2,292 | 153.0 | 152.0 | 10.1 | 14.85 | 1.5 | 16.4 | −6.3 | ..... | 800 | |
| Nov. 23 | ..... | 2,392 | 192.0 | 132.0 | 10.7 | 15.69 | 1.6 | 17.3 | −6.6 | ..... | 840 | |
| Nov. 24 | 2,282 | 2,016 | 173.0 | 117.0 | 8.5 | 13.08 | 1.3 | 14.4 | −5.9 | 46.98 | 890 | |
| Nov. 25 | 2,301 | 2,296 | 187.0 | 123.0 | 15.1 | 13.66 | 2.3 | 16.0 | −0.9 | 47.47 | 925 | |
| Nov. 26 | 2,217 | 2,087 | 172.0 | 126.0 | 8.0 | 10.32 | 1.2 | 11.5 | −3.5 | 45.84 | 780 | |
| Nov. 27 | ..... | 2,747 | 242.0 | 148.0 | 14.8 | 18.56 | 2.2 | 20.8 | −6.0 | ..... | 820 | |
| Nov. 28 | ..... | 2,741 | 256.0 | 140.0 | 15.0 | 12.44 | 2.3 | 14.7 | +0.3 | 47.26 | 980 | |
| Nov. 29 | ..... | 3,063 | 324.0 | 142.0 | 15.0 | 11.82 | 2.3 | 14.1 | +0.9 | ..... | 1,370 | |
| Nov. 30 | ..... | 3,153 | 334.0 | 147.0 | 16.0 | 10.76 | 2.4 | 13.2 | +2.8 | ..... | 1,060 | |
| Dec. 1 | ..... | 3,091 | 333.0 | 142.0 | 15.7 | 9.81 | 2.4 | 12.2 | +3.5 | 47.08 | 1,180 | |
| Dec. 2 | ..... | 3,060 | 340.0 | 142.0 | 15.3 | 9.69 | 2.3 | 12.0 | +3.3 | ..... | 1,060+ | |

* Feces analyzed October 30 to November 5. Feces nitrogen averaged 14.8 per cent. of food nitrogen. On all other days the feces nitrogen was calculated as 15 per cent. of food nitrogen.

TABLE 6.—CLINICAL DATA—(*Continued*)

MORRIS S.—(*Continued*)

| Date, 1913 | Estimated Heat Production per 24 Hrs. | Food | | | Food N., Gm. | Urine N., Gm. | Feces N., Gm.* | Excreta N., Gm.* | Nitrogen Balance, Gm. | Body Weight, Kg. | Urine Volume, C.c. | Feces Fat |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Total Calories | Carbohydrate, Gm. | Fat, Gm. | | | | | | | | |
| Dec. 3 | ..... | 3,189 | 356.0 | 141.0 | 16.0 | 8.52 | 2.4 | 10.9 | +5.1 | 47.31 | 930 | |
| Dec. 4 | ..... | 3,118 | 250.0 | 180.0 | 16.0 | 8.70 | 2.4 | 11.1 | +4.9 | ..... | 1,500 | |
| Dec. 5 | ..... | 2,977 | 156.0 | 209.0 | 15.0 | 8.74 | 2.3 | 11.0 | +4.0 | ..... | 1,520 | |
| Dec. 6 | .... | 2,998 | 161.0 | 209.0 | 15.0 | 9.75 | 2.3 | 12.1 | +2.9 | 46.55 | 1,340 | |
| Dec. 7 | ..... | 3,297 | 202.0 | 221.0 | 16.0 | 9.08 | 2.4 | 11.5 | +4.5 | ..... | 1,640 | |
| Dec. 8 | ..... | 3,914 | 206.0 | 289.0 | 14.9 | 8.55 | 2.2 | 10.8 | +4.1 | ..... | 1.340 | |
| Dec. 9 | ..... | 3,989 | 219.0 | 290.0 | 15.2 | 7.65 | 2.3 | 10.0 | +5.2 | 47.53 | 1,140 | |
| Dec. 10 | ..... | 3,989 | 219.0 | 290.0 | 15.2 | 8.85 | 2.3 | 11.2 | +4.0 | ..... | 1,550 | |
| Dec. 11 | ..... | 3,989 | 219.0 | 290.0 | 15.2 | 9.31 | 2.3 | 11.6 | +3.6 | 48.46 | 1,850 | |
| Dec. 12 | 1,857 | 3,552 | 222.0 | 226.0 | 21.3 | 9.87 | 3.2 | 13.1 | +8.2 | 48.64 | 1,700 | |
| Dec. 13 | 1,604 | 2,925 | 395.0 | 104.0 | 13.1 | 12.64 | 2.0 | 14.6 | —1.5 | 48.10 | 1,935 | |
| Dec. 14 | ..... | 3,256 | 475.0 | 95.0 | 16.5 | 9.47 | 2.5 | 12.0 | +4.5 | ..... | 1,100 | |
| Dec. 15 | 1,723 | 3,117 | 511.0 | 74.0 | 13.0 | 8.68 | 2.0 | 10.7 | +2.3 | 47.87 | 1,229 | |
| Dec. 16 | 1,703 | 2,132 | 275.0 | 76.0 | 11.6 | 10.24 | 1.7 | 11.9 | —0.3 | 47.91 | 802 | |
| Dec. 17 | ..... | 3,985 | 440.0 | 193.0 | 15.5 | 9.30 | 2.3 | 11.6 | +3.9 | ..... | 1,240 | |
| Dec. 18 | ..... | 3,499 | 256.0 | 224.0 | 14.4 | 10.82 | 2.2 | 13.0 | +1.4 | ..... | 1,670 | |
| Dec. 19 | 2,058 | 2,868 | 248.0 | 173.0 | 9.6 | 11.34 | 1.4 | 12.7 | —3.1 | 48.34 | 1,282 | |
| Dec. 20 | 2,061 | 2,748 | 150.0 | 190.0 | 14.1 | 13.41 | 2.1 | 15.5 | —1.4 | 48.55 | 1,343 | |
| Dec. 21 | ..... | 3,426 | 204.0 | 232.0 | 16.0 | 17.32 | 2.4 | 19.7 | —3.7 | 48.55 | 1,560 | |
| Dec. 22 | 2,217 | 3,034 | 345.0 | 140.0 | 12.2 | 14.42 | 1.8 | 16.2 | —4.0 | 48.50 | 1,223 | |
| Dec. 23 | 1,982 | 2,499 | 121.0 | 186.0 | 10.7 | 11.94 | 1.6 | 13.5 | —2.8 | 48.54 | 883 | |
| Dec. 24 | ..... | 3,357 | 206.0 | 225.0 | 16.5 | 13.06 | 2.5 | 15.6 | +0.9 | ..... | 1,480 | |
| Dec. 25 | ..... | ..... | ..... | ..... | .... | 10.90 | ... | .... | ..... | ..... | 1,200 | |
| Dec. 26 | ..... | 3,560 | 189.0 | 253.0 | 17.1 | 10.48 | 2.6 | 13.1 | +4.0 | 49.70 | 1,680 | |
| Dec. 27 | ..... | 3,180 | 159.0 | 227.0 | 16.4 | 11.10 | 2.5 | 13.6 | +2.8 | ..... | 1,930 | |
| Dec. 28 | ..... | 3,128 | 157.0 | 224.0 | 15.5 | 11.43 | 2.3 | 13.7 | +1.8 | ..... | 1,740 | |
| Dec. 29 | ..... | 3,109 | 157.0 | 222.0 | 15.5 | 11.77 | 2.3 | 14.1 | +1.4 | ..... | 1,380 | |
| Dec. 30 | ..... | 3,277 | 170.0 | 235.0 | 15.5 | 11.72 | 2.3 | 14.0 | +1.5 | ..... | 1,710 | |
| Dec. 31 | ..... | 2,990 | 293.0 | 143.0 | 17.9 | 12.61 | 2.7 | 15.3 | +2.6 | ..... | 1,600 | |
| 1914 Jan. 1 | ..... | 2,991 | 256.0 | 166.0 | 15.4 | 12.11 | 2.3 | 14.4 | +1.0 | ..... | 2,120 | |
| Jan. 2 | 1,567 | 2,078 | 141.0 | 132.0 | 10.7 | 10.01 | 1.6 | 11.6 | —0.9 | 49.22 | 1,340 | |
| Jan. 3 | ..... | 3,051 | 158.0 | 216.0 | 15.6 | 12.27 | 2.3 | 14.6 | +1.0 | ..... | 2,160 | |
| Jan. 4 | ..... | 3,070 | 162.0 | 216.0 | 15.7 | 10.40 | 2.4 | 12.8 | +2.9 | ..... | 1,730 | |
| Jan. 5 | ..... | ..... | ..... | ..... | .... | 11.21 | ... | .... | ..... | ..... | 1,580 | |
| Jan. 6 | ..... | 3,044 | 158.0 | 215.0 | 15.5 | 12.69 | 2.3 | 15.0 | +0.5 | ..... | 2,330 | |
| Jan. 7 | ..... | 3,045 | 158.0 | 215.0 | 15.5 | 11.66 | 2.3 | 14.0 | +1.5 | ..... | 1,800 | |
| Jan. 8 | ..... | 3,068 | 162.0 | 215.0 | 15.6 | 11.77 | 2.3 | 14.1 | +1.5 | ..... | 1,460 | |
| Jan. 9 | ..... | 3,063 | 162.0 | 215.0 | 15.6 | 11.66 | 2.3 | 14.0 | +1.6 | ..... | 1,660 | |
| Jan. 10 | ..... | 3,475 | 268.0 | 208.0 | 17.3 | 12.10 | 2.6 | 14.7 | +2.6 | ..... | 1,460 | |
| Jan. 11 | ..... | 3,739 | 354.0 | 191.0 | 19.8 | 12.22 | 3.0 | 15.2 | +4.6 | ..... | 1,560 | |
| Jan. 12 | ..... | 3,551 | 344.0 | 177.0 | 19.5 | 12.61 | 2.9 | 15.5 | +4.0 | ..... | 2,350 | |
| Jan. 13 | ..... | 4,196 | 382.0 | 222.0 | 22.1 | 11.49 | 3.3 | 14.8 | +7.3 | ..... | 1,520 | |

* Excreta nitrogen estimated as urine nitrogen + 15 per cent of food nitrogen.

TABLE 6.—Clinical Data—(*Continued*)

Howard F.

| Date, 1913 | Food | | | Food N., Gm. | Urine N., Gm. | Excreta N., Gm. | Nitrogen Bal., Gm.* | Body Wt., Kg. | Urine Vol., C.c. |
|---|---|---|---|---|---|---|---|---|---|
| | Total Calories | Carbohydrate, Gm. | Fat, Gm. | | | | | | |
| Nov. 6.... | 1,264 | 83.0 | 81.0 | 6.7 | 12.82 | 13.50 | −6.80 | 36.06 | 970 |
| Nov. 7.... | 913 | 62.0 | 59.0 | 4.4 | 12.05 | 12.49 | −8.09 | 35.74 | 640 |
| Nov. 8.... | 1,538 | 87.0 | 107.0 | 7.0 | 12.75 | 13.45 | −6.45 | 35.79 | 840 |
| Nov. 9.... | 1,454 | 106.0 | 88.0 | 7.7 | 12.61 | 13.38 | −5.68 | ..... | 700 |
| Nov. 10.... | 1,401 | 115.0 | 78.0 | 8.1 | 12.67 | 13.48 | −5.38 | ..... | 680 |
| Nov. 11.... | 925 | 93.0 | 38.0 | 7.5 | 13.79 | 14.54 | −7.04 | 34.60 | 750 |
| Nov. 12.... | 959 | 98.0 | 40.0 | 7.3 | 13.42 | 14.15 | −6.85 | 35.01 | 830 |
| Nov. 13.... | 1,260 | 134.0 | 60.0 | 5.8 | 12.52 | 13.10 | −7.30 | 34.22 | 610 |
| Nov. 14.... | 580 | 52.0 | 30.0 | 2.4 | 10.42 | 10.76 | −7.36 | ..... | 500 |
| Nov. 15.... | 1,132 | 82.0 | 69.0 | 6.6 | 11.10 | 11.76 | −5.16 | 33.36 | 900 |
| Nov. 16.... | 1,006 | 100.0 | 40.0 | 4.4 | 9.98 | 10.42 | −6.02 | ..... | 500 |
| Nov. 17.... | 1,402 | 123.0 | 83.0 | 7.2 | 9.30 | 10.02 | −2.82 | 33.12 | 400 |
| Nov. 18.... | 1,558 | 138.0 | 91.0 | 8.5 | 10.50 | 11.05 | −2.55 | 32.93 | 590 |
| Nov. 19.... | 984 | 63.0 | 62.0 | 5.7 | 10.65 | 11.22 | −5.52 | ..... | 780 |
| Nov. 20.... | 1,288 | 74.0 | 75.0 | 7.5 | 10.25 | 10.96 | −3.68 | 32.57 | 550 |
| Nov. 21.... | 1,466 | 91.0 | 95.0 | 8.1 | 11.32 | 12.13 | −4.03 | ..... | 700 |
| Nov. 22.... | 1,196 | 72.0 | 94.0 | 8.8 | 11.12 | 12.00 | −3.20 | ..... | 800 |
| Nov. 23.... | 1,789 | 92.0 | 121.0 | 11.6 | 11.15 | 12.31 | −0.71 | ..... | 660 |
| Nov. 24.... | 1,846 | 146.0 | 145.0 | 10.6 | 10.82 | 11.88 | −1.28 | ..... | 820 |
| Nov. 25.... | 2,060 | 138.0 | 129.0 | 11.4 | 9.81 | 10.95 | +0.45 | 32.14 | 940 |
| Nov. 26.... | 2,686 | 176.0 | 168.0 | 15.7 | 10.42 | 11.99 | +3.71 | ..... | 780 |
| Nov. 27.... | 2,240 | 211.0 | 118.0 | 10.9 | 9.47 | 10.56 | +0.34 | ..... | 570 |
| Nov. 28.... | 2,742 | 245.0 | 145.0 | 13.0 | 9.98 | 11.48 | +3.52 | 32.25 | 960 |
| Nov. 29.... | 2,581 | 211.0 | 152.0 | 11.9 | 8.82 | 9.71 | +2.19 | ..... | 620 |
| Nov. 30.... | 2,922 | 273.0 | 153.0 | 14.8 | 9.53 | 11.01 | +3.79 | ..... | 1,220 |
| Dec. 1.... | 2,581 | 209.0 | 112.0 | 10.6 | 7.77 | 8.82 | +1.77 | ..... | 870 |
| Dec. 2.... | 2,298 | 247.0 | 110.0 | 10.0 | 7.69 | 8.69 | +1.31 | 33.09 | 900 |
| Dec. 3.... | 3,689 | 423.0 | 163.0 | 17.2 | 9.25 | 10.97 | +6.23 | ..... | 900 |
| Dec. 4.... | 3,627 | 441.0 | 147.0 | 17.7 | 9.00 | 10.77 | +6.93 | ..... | 1,130 |
| Dec. 5.... | 2,671 | 337.0 | 81.0 | 21.0 | 13.01 | 15.11 | +5.89 | 34.77 | 1,500 |
| Dec. 6.... | 2,476 | 333.0 | 83.0 | 12.9 | 9.30 | 10.49 | +2.41 | 33.81 | 775 |
| Dec. 7.... | 3,621 | 406.0 | 119.0 | 19.0 | 10.45 | 12.25 | +6.65 | ..... | 1,500 |
| Dec. 8.... | 3,291 | 434.0 | 112.0 | 17.8 | 9.89 | 11.67 | +6.13 | ..... | 1,570+ |
| Dec. 9.... | 3,042 | 386.0 | 106.0 | 18.0 | 10.73 | 12.53 | +5.47 | 35.51 | 1,300 |
| Dec. 10.... | 2,966 | 294.0 | 101.0 | 16.8 | 10.51 | 12.19 | +4.61 | ..... | 1,450 |
| Dec. 11.... | 3,140 | 405.0 | 114.0 | 17.8 | 10.79 | 12.67 | +5.22 | 35.90 | 1,450 |
| Dec 12.... | 3,100 | 417.0 | 101.0 | 17.5 | 10.36 | 12.11 | +5.39 | ..... | 1,610 |
| Dec. 13.... | 3,544 | 472.0 | 122.0 | 18.5 | 10.03 | 11.88 | +6.62 | 36.05 | 1,280 |

TABLE 6.—Clinical Data—(*Continued*)

Howard F.—(*Continued*)

| Date, 1913 | Food | | | Food N., Gm. | Urine N., Gm. | Excreta N., Gm. | Nitrogen Bal., Gm.* | Body Wt., Kg. | Urine Vol., C.c. |
|---|---|---|---|---|---|---|---|---|---|
| | Total Calories | Carbohydrate, Gm. | Fat, Gm. | | | | | | |
| Dec. 14.... | 3,338 | 402.0 | 133.0 | 17.8 | 11.01 | 12.79 | +5.01 | ..... | 1,880 |
| Dec. 15.... | 3,280 | 510.0 | 130.0 | 19.2 | 12.98 | 14.90 | +4.30 | 37.54 | 1,890+ |
| Dec. 16.... | 3,511 | 444.0 | 129.0 | 19.2 | 13.28 | 15.20 | +4.00 | ..... | 1,580 |
| Dec. 17.... | 3,170 | 345.0 | 139.0 | 18.0 | 9.95 | 11.75 | +6.25 | 39.10 | 1,720 |
| Dec. 18.... | 2,008 | 248.0 | 78.0 | 10.5 | 8.57 | 9.62 | +0.88 | 37.17 | 1,600 |
| Dec. 19.... | 3,550 | 411.0 | 144.0 | 20.3 | 11.89 | 13.92 | +6.38 | ..... | 2.050 |
| Dec. 20.... | 2,671 | 110.0 | 197.0 | 15.0 | 8.10 | 9.60 | +5.40 | ..... | 1,540 |
| Dec. 21.... | 2,383 | 104.0 | 175.0 | 12.6 | 10.65 | 11.91 | +0.69 | ..... | 1,250 |
| Dec. 22.... | 2,936 | 159.0 | 198.0 | 17.2 | 13.23 | 14.96 | +2.34 | 37.21 | 1,150 |
| Dec. 23.... | 3,520 | 239.0 | 235.0 | 13.9 | 9.19 | 10.58 | +3.32 | ..... | 1,200 |
| Dec 24.... | 3,605 | 219.0 | 243.0 | 17.4 | 10.70 | 12.44 | +4.96 | ..... | 1,700 |
| Dec. 25.... | ..... | ..... | ..... | .... | 10.42 | ..... | ..... | ..... | 1,370 |
| Dec. 26.... | 3,152 | 219.0 | 199.0 | 15.6 | 9.77 | 11.33 | +4.27 | 39.46 | 2,100 |
| Dec. 27.... | 3,303 | 257.0 | 196.0 | 16.8 | 10.03 | 11.71 | +5.09 | ..... | 1.600 |
| Dec. 28.... | 2,946 | 200.0 | 186.0 | 15.4 | 7.51 | 9.05 | +6.35 | ..... | 1.080 |
| Dec. 29.... | 4,199 | 265.0 | 278.0 | 20.5 | 10.87 | 12.92 | +7.58 | ..... | 1,640 |
| Dec. 30.... | 2,325 | 165.0 | 145.0 | 11.4 | 7.81 | 8.95 | +2.45 | 39.39 | 987 |
| Dec. 31.... | 3,569 | 317.0 | 192.0 | 18.5 | 11.77 | 13.62 | +4.88 | ..... | 1,500 |
| 1914 Jan. 1.... | 2,912 | 236.0 | 169.0 | 14.5 | 9.02 | 10.47 | +4.03 | ..... | 1,600 |
| Jan. 2.... | 2,891 | 224.0 | 156.0 | 16.0 | 8.74 | 10.34 | +5.66 | ..... | 1,540 |

* Excreta nitrogen estimated as urine nitrogen + 10 per cent of food nitrogen.

TABLE 6.—Clinical Data—(*Continued*)

TABLE 6.—Clinical Data—(*Continued*)

Karl S.

| Date, 1914 | Estimated Heat Production per 24 Hrs. | Food | | | Food N., Gm. | Urine N., Gm. | Feces N., Gm. | Excreta N., Gm.* | Nitrogen Balance, Gm. | Body Weight, Kg. | Urine Volume, C.c. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Total Calories | Carbohydrate, Gm. | Fat, Gm | | | | | | | |
| Jan. 3 | ..... | 2,038 | 104.0 | 145.0 | 10.8 | 20.52 | ... | 21.60 | —10.80 | ..... | 880 |
| Jan. 4 | ..... | 1,301 | 113.0 | 71.0 | 6.9 | 21.72 | ... | 22.41 | —15.51 | ..... | 1,240 |
| Jan. 5 | 2,579 | 1,119 | 95.0 | 64.0 | 5.4 | ..... | ... | ..... | ..... | 54.67 | 725 |
| Jan. 6 | 2,707 | 1,332 | 167.0 | 32.0 | 13.6 | 22.36 | ... | 23.72 | —10.12 | 54.31 | 1,010 |
| Jan. 7 | ..... | 1,942 | 93.2 | 136.0 | 11.2 | ..... | ... | ..... | ..... | ..... | 810 |
| Jan. 8 | ..... | 2,331 | 136.0 | 156.0 | 12.5 | 16.03 | ... | 17.28 | —4.78 | ..... | 860 |
| Jan. 9 | ..... | 1,892 | 114.0 | 126.0 | 9.8 | 23.84 | ... | 24.82 | —15.02 | 52.90 | 1,700 |
| Jan. 10 | ..... | 2,910 | 222.0 | 174.0 | 14.6 | | | | | | |
| Jan. 11 | ..... | 3,018 | 318.0 | 120.0 | 16.4 | | | | | | |
| Jan. 12 | ..... | 3,017 | 322.0 | 138.0 | 16.2 | 18.15 | 1.6 | 19.8 | —3.6 | ..... | 2,310 |
| Jan. 13 | ..... | 2,966 | 326.0 | 128.0 | 17.2 | 13.94 | 1.7 | 15.6 | +1.6 | ..... | 1,820 |
| Jan. 14 | ..... | 2,802 | 313.0 | 118.0 | 16.4 | 17.06 | 1.6 | 18.7 | —2.3 | ..... | 1,830 |
| Jan. 15 | ..... | 3,129 | 322.0 | 149.0 | 16.2 | 15.65 | 1.6 | 20.3 | —4.1 | 52.74 | 1,920 |
| Jan. 16 | 2,208 | 2,448 | 296.0 | 122.0 | 11.5 | 19.11 | 1.2 | 20.3 | —8.8 | 52.24 | 1,960 |
| Jan. 17 | ..... | 3,206 | 340.0 | 166.0 | 17.9 | 19.16 | 1.8 | 21.0 | —3.1 | ..... | 1,940 |
| Jan. 18 | ..... | 3,138 | 329.0 | 145.0 | 17.1 | 17.26 | 1.7 | 19.0 | —1.9 | ..... | 1,920 |
| Jan. 19 | 1,651 | 2,795 | 266.0 | 145.0 | 13.6 | 14.72 | 1.4 | 16.1 | —2.5 | 51.21 | 1,280 |
| Jan. 20 | ..... | 2,965 | 313.0 | 138.0 | 15.7 | 14.51 | 1.6 | 16.1 | —0.4 | ..... | 1,550 |
| Jan. 21 | 1,798 | 2,912 | 315.0 | 129.0 | 16.3 | 17.57 | 1.6 | 19.2 | —2.9 | 51.52 | 1,870 |
| Jan. 22 | 1,512 | 2,605 | 253.0 | 133.0 | 12.8 | 13.25 | 1.3 | 14.6 | —1.8 | 51.18 | 1,194 |
| Jan. 23 | ..... | 3,063 | 324.0 | 140.0 | 15.9 | 11.90 | 1.6 | 13.6 | +2.3 | ..... | 1,360 |
| Jan. 24 | ..... | 2,982 | 315.0 | 138.0 | 15.8 | 13.00 | 1.6 | 14.7 | +1.1 | ..... | 1,960 |
| Jan. 25 | ..... | 2,987 | 315.0 | 139.0 | 15.8 | 13.17 | 1.6 | 14.8 | +1.0 | ..... | 1,400 |
| Jan. 26 | ..... | 3,541 | 408.0 | 155.0 | 16.7 | 12.64 | 1.7 | 14.3 | +2.4 | 54.64 | 1,620 |
| Jan. 27 | ..... | 3,960 | 439.0 | 191.0 | 16.3 | 13.06 | 1.6 | 14.7 | +1.6 | ..... | 1,460 |
| Jan. 28 | ..... | 4,025 | 439.0 | 194.0 | 16.3 | 11.86 | 1.6 | 13.5 | +2.8 | ..... | 1,280 |
| Jan. 29 | ..... | 3,975 | 438.0 | 190.0 | 16.1 | 11.32 | 1.6 | 12.9 | +3.2 | 52.54 | 1,450 |
| Jan. 30 | ..... | 3,991 | 439.0 | 191.0 | 16.2 | 10.65 | 1.6 | 12.3 | +3.9 | ..... | 1,500 |
| Jan. 31 | ..... | 3,922 | 418.0 | 198.0 | 16.2 | 10.93 | 1.6 | 12.5 | +3.7 | ..... | 1,400 |
| Feb. 1 | ..... | 3,940 | 418.0 | 194.0 | 16.3 | 10.63 | 1.6 | 12.2 | +4.1 | ..... | 1,500 |
| Feb. 2 | ..... | 3,808 | 419.0 | 180.0 | 16.0 | 11.21 | 1.6 | 12.8 | +3.2 | ..... | 1,910 |
| Feb. 3 | ..... | 3,808 | 419.0 | 180.0 | 16.0 | 11.15 | 1.6 | 12.8 | +3.2 | ..... | 1,980 |
| Feb. 4 | ..... | 3,971 | 442.0 | 188.0 | 16.0 | 10.87 | 1.6 | 12.5 | +3.5 | ..... | 1,870 |
| Feb. 5 | ..... | 3,974 | 438.0 | 191.0 | 16.0 | 9.29 | 1.6 | 10.9 | +5.1 | ..... | 1,640 |
| Feb. 6 | 1,916 | 3,222 | 330.0 | 165.0 | 13.3 | 10.24 | 1.3 | 11.5 | +1.8 | 53.33 | 1,360 |
| Feb. 7 | 1,965 | 3,526 | 387.0 | 148.0 | 22.1 | ..... | 2.2 | 17.3 | +4.8 | 54.48 | 2,300 |
| Feb. 8 | ..... | 4,018 | 474.0 | 178.0 | 16.3 | 11.67 | 1.6 | 13.3 | +3.0 | ..... | 1,440 |

* Excreta nitrogen estimated as urine nitrogen + 10 per cent. of food nitrogen.

TABLE 6.—Clinical Data—(*Continued*)

TABLE 6.—Clinical Data—(*Continued*)

Thomas B.

| Date 1913 | Temperature | | Food | | | Food N., Gm. | Urine N., Gm. | Feces N., Gm. | Excreta N., Gm. | Nitrogen Balance, Gm. | Body Weight, Kg. | Urine Volume, C.c. | Feces Fat |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Max. | Min. | Total Calories | Carbohydrate, Gm. | Fat, Gm. | | | | | | | | |
| Oct. 7 | 103.0 | 101.4 | 3,052 | 168.0 | 212.0 | 15.0 | 24.55 | 2.09 | 26.64 | −11.64 | 76.08 | 1,240 | 9.19 |
| Oct. 8 | 103.6 | 101.2 | 3,010 | 163.0 | 210.0 | 15.0 | 25.50 | 2.09 | 27.59 | −12.59 | 75.61 | 1,270 | 9.19 |
| Oct. 9 | 104.0 | 101.6 | 3,010 | 163.0 | 210.0 | 15.0 | 21.29 | 2.09 | 23.38 | −8.38 | 75.73 | 1,120 | 9.19 |
| Oct. 10 | 103.6 | 101.6 | 3,030 | 163.0 | 212.0 | 15.0 | 23.67 | 2.09 | 25.76 | −10.76 | 76.02 | 1,740 | 9.19 |
| Oct. 11 | 103.0 | 101.0 | 3,014 | 479.0 | 71.0 | 14.9 | 20.12 | 1.89 | 22.01 | −7.11 | 74.85 | 1,500 | 5.80 |
| Oct. 12 | 102.8 | 101.6 | 3,018 | 480.0 | 71.0 | 15.0 | 17.77 | 1.89 | 19.66 | −4.66 | ..... | 1,950 | 5.80 |
| Oct. 13 | 102.4 | 100.6 | 3,014 | 479.0 | 71.0 | 14.9 | 18.77 | 1.89 | 20.66 | −5.76 | 74.24 | 1,980 | 5.80 |
| Oct. 14 | 103.0 | 100.0 | 3,045 | 173.0 | 212.0 | 14.2 | 18.21 | 1.28 | 19.49 | −5.29 | 74.38 | 1,220 | 5.02 |
| Oct. 15 | 102.2 | 96.6 | 2,570 | 130.0 | 187.0 | 11.7 | 18.61 | 1.28 | 19.89 | −8.19 | ..... | 1,040 | 5.02 |
| Oct. 16 | 101.0 | 99.4 | 3,058 | 166.0 | 212.0 | 15.4 | 21.04 | 1.28 | 22.32 | −6.92 | ..... | 1,010 | 5.02 |
| Oct. 17 | 101.6 | 99.4 | 3,211 | 484.0 | 78.0 | 15.6 | 17.79 | .... | 19.35* | −3.75 | 73.10 | 1,120 | |
| Oct. 18 | 100.6 | 99.0 | 2,986 | 476.0 | 71.0 | 15.0 | 15.69 | .... | 17.19 | −2.19 | ..... | 1,100 | |
| Oct. 19 | 99.6 | 98.6 | 3,019 | 481.0 | 71.0 | 15.0 | 15.30 | .... | 16.80 | −1.80 | ..... | 1,220 | |
| Oct. 20 | 99.6 | 98.6 | 3,002 | 468.0 | 75.0 | 15.0 | 15.24 | .... | 16.74 | −1.74 | 72.82 | 1,880 | |
| Oct. 21 | 98.6 | 99.4 | 2,675 | 412.0 | 68.0 | 13.0 | 15.75† | .... | ..... | ..... | ..... | 1,610+ | (?) |
| Oct. 22 | 99.6 | 98.8 | 2,943 | 462.0 | 71.0 | 15.0 | 16.32 | .... | 17.82 | −2.82 | ..... | 1,480 | |
| Oct. 23 | 99.6 | 98.6 | 3,062 | 449.0 | 76.0 | 21.2 | 16.76 | .... | 18.88 | +2.32 | ..... | 1,230 | |
| Oct. 24 | 99.6 | 98.6 | 3,396 | 541.0 | 60.0 | 20.0 | 13.34 | .... | 15.34 | +4.66 | 72.86 | 1,640 | |
| Oct. 25 | 99.6 | 98.6 | 3,211 | 493.0 | 71.0 | 20.0 | 16.59 | .... | 18.59 | +1.41 | ..... | 1,120 | |
| Oct. 26 | 99.0 | 98.2 | 3,066 | 164.0 | 215.0 | 15.5 | 18.90 | .... | 20.45 | −4.95 | ..... | 1,320 | |
| Oct. 27 | 99.6 | 98.4 | 3,159 | 164.0 | 219.0 | 17.5 | 17.65 | .... | 19.40 | −1.90 | ..... | 2,280 | |
| Oct. 28 | 99.0 | 98.2 | 3,277 | 182.0 | 220.0 | 18.5 | 14.18 | .... | 16.03 | +2.47 | 73.69 | 1,220 | |

† This is the total for 19¾ hours.

* Excreta nitrogen estimated as urine nitrogen + 10 per cent. of food nitrogen.

TABLE 6.—Clinical Data—(*Continued*)

Richard T.

| Date 1913 | Temperature | | Food | | | Food N., Gm. | Urine N., Gm. | Feces N., Gm. | Excreta N., Gm. | Nitrogen Balance, Gm. | Body Weight, Kg. | Urine Volume, C.c. | Feces Fat |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Max. | Min. | Total Calories | Carbohydrate, Gm. | Fat, Gm. | | | | | | | | |
| Oct. 17 | 103.6 | 101.4 | 1,656 | 248.0 | 38.0 | 11.3 | 13.95 | 0.84 | 14.79 | −3.49 | 36.09 | 2,290 | 1.63 |
| Oct. 18 | 104.2 | 100.8 | 1,143 | 115.0 | 49.0 | 8.4 | 12.48 | 0.84 | 13.32 | −4.92 | ..... | 1,145 | 1.63 |
| Oct. 19 | 103.2 | 100.8 | 2,131 | 327.0 | 49.0 | 13.0 | 14.40 | 0.84 | 15.24 | −2.24 | ..... | 1,720 | 1.63 |
| Oct. 20 | 104.0 | 100.0 | 2,020 | 280.0 | 55.0 | 14.0 | 14.53 | 0.84 | 15.37 | −1.37 | ..... | 1,005 | 1.63 |
| Oct. 21 | 102.8 | 100.0 | 2,359 | 360.0 | 51.0 | 16.0 | 15.13 | 0.84 | 15.97 | +0.03 | ..... | 1,320 | 1.63 |
| Oct. 22 | 102.4 | 99.4 | 2,092 | 315.0 | 46.0 | 14.7 | 14.74 | 0.84 | 15.58 | −0.88 | 35.57 | 1,200 | 1.63 |
| Oct. 23 | 103.0 | 99.0 | 2,576 | 369.0 | 67.0 | 17.4 | 16.30 | 0.84 | 17.14 | +0.26 | 35.70 | 1,570 | 1.63 |
| Oct. 24 | 102.0 | 99.4 | 2,153 | 333.0 | 35.0 | 18.0 | 15.69 | 0.84 | 16.53 | +1.47 | ..... | 1,340 | 1.63 |
| Oct. 25 | 101.0 | 98.4 | 2,519 | 228.0 | 125.0 | 16.0 | 16.32 | 0.84 | 17.16 | −1.16 | ..... | 1,260 | 1.63 |
| Oct. 26 | 100.6 | 99.0 | 2,093 | 115.0 | 133.0 | 15.0 | 16.53 | .... | * 18.03 | −3.03 | ..... | 1,100 | |
| Oct. 27 | 100.2 | 98.6 | 2,163 | 121.0 | 136.0 | 15.7 | 16.34 | .... | 17.91 | −2.21 | 35.30 | 1,300 | |
| Oct. 28 | 99.6 | 98.6 | 2,009 | 124.0 | 117.0 | 16.0 | 16.47 | .... | 18.07 | −2.07 | 35.60 | 1,460 | |
| Oct. 29 | 100.0 | 98.6 | 2,276 | 346.0 | 157.0 | 15.2 | 14.01 | .... | 15.53 | −0.33 | ..... | 1,370 | |
| Oct. 30 | 100.0 | 99.0 | 2,969 | 302.0 | 144.0 | 15.1 | 11.77 | .... | 13.28 | +1.82 | 35.38 | 1,195 | |
| Oct. 31 | 101.6 | 99.2 | 2,954 | 310.0 | 142.0 | 15.5 | 12.05 | .... | 13.60 | +1.90 | ..... | 1,420 | |
| Nov. 1 | 102.0 | 100.4 | 2,969 | 324.0 | 142.0 | 14.5 | 11.32 | .... | 12.77 | +1.73 | 36.08 | 1,320 | |
| Nov. 2 | 102.4 | 99.6 | 2,995 | 325.0 | 138.0 | 14.5 | 11.74 | .... | 13.19 | +1.31 | ..... | 1,900 | |
| Nov. 3 | 101.0 | 99.6 | 2,984 | 316.0 | 140.0 | 15.1 | 11.99 | .... | 13.50 | +1.60 | 36.27 | 1,270 | |
| Nov. 4 | 100.2 | 99.4 | 3,037 | 320.0 | 144.0 | 15.2 | 12.22 | .... | 13.74 | +1.46 | 36.42 | 1,560 | |

* Excreta nitrogen estimated as urine nitrogen + 10 per cent. of food nitrogen.

TABLE 6.—Clinical Data—(*Continued*)
Edward B.

| Date, 1914 | Estimated Heat Production per 24 Hrs. | Food | | | Food N., Gm. | Urine N., Gm. | Excreta N., Gm.* | Nitrogen Balance Gm. | Body Weight, Kg. | Urine Volume, C.c. |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Total Calories | Carbohydrate, Gm. | Fat, Gm. | | | | | | |
| Oct. 14 | ..... | 3,901 | 214.9 | 284.8 | 14.5 | 14.51 | 15.96 | −1.46 | 56.29 | 1,180 |
| Oct. 15 | ..... | 4,171 | 212.9 | 309.3 | 16.4 | 11.39 | 13.03 | +3.4 | ..... | 1.415 |
| Oct. 16 | ..... | 4,008 | 662.0 | 97.2 | 15.0 | 11.49 | 12.99 | +2.0 | 56.36 | 1,665(?) |
| Oct. 17 | ..... | 1,561 | 226.3 | 43.8 | 7.28 | 8.65 | 9.37 | −2.09 | 56.94 | 1,140 |
| Oct. 18 | ..... | 2,976 | 94.5 | 236.9 | 15.0 | 11.08 | 12.58 | −2.42 | 56.01 | 1,690 |
| Oct. 19 | ..... | 4,217 | 111.0 | 362.1 | 13.9 | 16.17 | 17.56 | −3.66 | 56.98 | 2,230 |
| Oct. 20 | ..... | 4,097 | 114.9 | 348.9 | 14.80 | 10.96 | 12.44 | +2.36 | 56.57 | 1.520 |
| Oct. 21 | ..... | 3,586 | 518.9 | 114.7 | 15.20 | 9.17 | 10.69 | +4.51 | 57.21 | 1,250 |
| Oct. 22 | ..... | 3,076 | 579.6 | 54.2 | 7.68 | 7.85 | 8.61 | −0.93 | 56.60 | 1,170 |
| Oct. 23 | 2,160 | 3,462 | 152.8 | 269.1 | 12.90 | 8.21 | 9.50 | +3.40 | 55.76 | 835 |
| Oct. 24 | ..... | 4,072 | 220.6 | 299.4 | 15.0 | 11.94 | 13.44 | +1.56 | 56.84 | 1,465 |
| Oct. 25 | ..... | 4,114 | 220.9 | 303.1 | 15.1 | 11.20 | 12.70 | +2.40 | 56.73 | 1,515 |
| Oct. 26 | 1,976 | 2,704 | 151.4 | 124.1 | 6.9 | 6.75 | 7.44 | −0.54 | ..... | 663 |
| Oct. 27 | 1,982 | 3,844 | 109.1 | 334.5 | 11.1 | 8.61 | 9.72 | +1.38 | ..... | 1,125 |
| Oct. 28 | ..... | 4,056 | 223.4 | 295.7 | 15.2 | 8.19 | 9.71 | +5.49 | 57.51 | 2,155 |
| Oct. 29 | ..... | 4,185 | 314.8 | 265.7 | 16.5 | 8.70 | 10.35 | +6.15 | 57.46 | 1,960 |
| Oct. 30 | ..... | 3,643 | 364.7 | 179.0 | 18.8 | 10.30 | 12.18 | +6.62 | 57.83 | 2.310 |
| Oct 31 | ..... | 3,893 | 402.5 | 191.4 | 18.0 | 9.72 | 11.52 | +6.48 | ..... | 1.655 |
| Nov. 1 | ..... | 4,394 | 455.7 | 218.4 | 19.3 | 11.05 | 12.98 | +6.32 | 58.53 | 2,450 |
| Nov. 2 | ..... | 4,491 | 451.6 | 225.8 | 21.0 | 11.80 | 13.9 | +7.1 | 58.76 | 1,770 |
| Nov. 3 | ..... | 4,836 | 491.9 | 244.6 | 21.2 | 12.20 | 14.32 | +6.88 | 59.52 | 2,405 |
| Nov. 4 | 1,986 | 2,209 | 209.4 | 119.7 | 9.2 | 9.20 | 10.12 | −0.92 | ..... | 979 |
| Nov. 5 | ..... | 3,960 | 390.5 | 195.9 | 17.0 | 10.59 | 12.29 | +5.71 | ..... | 1,665 |
| Nov. 6 | 2,117 | 1,907 | 219.5 | 85.9 | 8.0 | 10.96 | 11.76 | −3.76 | ..... | 1,523 |
| Nov. 7 | ..... | 1,006 | 101.2 | 49.8 | 5.05 | 12.13 | 12.63 | −7.58 | 59.23 | 1.075 |
| Nov. 8 | ..... | 296 | 64.0 | 11.8 | 1.08 | 10.34 | 10.44 | −9.36 | ..... | 665 |
| Nov. 9 | ..... | 617 | 94.8 | 20.0 | 1.68 | 11.26 | 11.42 | −9.74 | 57.06 | 645 |
| Nov. 10 | 2,632 | 1,108 | 104.3 | 51.2 | 6.0 | 14.72 | 15.32 | −9.32 | ..... | 833 |
| Nov. 11 | ..... | 1,646 | 96.0 | 84.2 | 9.7 | 16.73 | 17.70 | −8.0 | 57.11 | 1,230 |
| Nov. 12 | ..... | 2,196 | 165.9 | 119.3 | 10.7 | 14.79 | 15.8 | −5.1 | ..... | 1,250 |

* Excreta nitrogen estimated as urine nitrogen + 10 per cent. of food nitrogen.

TABLE 6.—Clinical Data—(*Continued*)
John K.

| Date, 1913 | Total Calories | Carbohydrate, Gm. | Fat, Gm. | Food N., Gm. | Urine N., Gm. | Excreta N., Gm. | Nitrogen Bal., Gm. | Body Wt., Kg. | Urine Vol., C.c. |
|---|---|---|---|---|---|---|---|---|---|
| Dec. 15.... | * 2,194 | 139.1 | 148.9 | 9.3 | 24.58 | 25.51 | −16.21 | 63.81 | 1,152 |
| Dec. 16.... | 3,309 | 145.1 | 246.8 | 16.3 | 21.45 | 23.08 | −6.78 | 63.55 | 1,180 |
| Dec. 17.... | 3,521 | 181.9 | 258.1 | 14.6 | 22.37 | 23.83 | −9.23 | 63.27 | 3,110 |
| Dec. 18.... | 3,205 | 181.9 | 223.6 | 14.8 | 19.30 | 20.78 | −5.98 | 63.35 | 3,040 |
| Dec. 19.... | 3,788 | 251.6 | 249.6 | 17.0 | 19.40 | 21.10 | −4.10 | 63.05 | 3,230 |
| Dec. 20.... | 3,916 | 259.7 | 257.1 | 18.0 | 18.26 | 20.06 | −2.06 | 62.37 | 3,460 |
| Dec. 21.... | 4,134 | 342.5 | 238.4 | 20.0 | 19.33 | 21.33 | −1.33 | 63.04 | 4,285 |
| Dec. 22.... | 4,558 | 378.4 | 267.2 | 20.4 | 18.00 | 20.04 | +0.36 | 62.64 | 4,255 |
| Dec. 23.... | 4,838 | 298.9 | 285.8 | 22.0 | 17.93 | 22.13 | −0.13 | 62.26 | 3,210 |
| Dec. 24.... | 4,450 | 373.1 | 259.1 | 19.9 | 18.78 | 20.77 | −0.87 | 62.32 | 3,350 |

* Estimated heat production, 2,568 calories.

TABLE 7.—Summary of Clinical Calorimetry in Typhoid Fever

| Subject and Date | Character of Experiment | Period of Disease | Average Rectal Temp. C. | Average Pulse Rate | Average Respiratory Quotient | Indirect Calorimetry Average per Hour | | Per Cent. Divergence of Direct Cal. from Indirect Calories | | Per Cent. Rise Above Normal Aver. Basal of 34.7 Cal. per Sq. M. | Per Cent. Rise Above Patient's Own Basal Metabolism | Day of Basal Determination Used for Comparison |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Cal. per Kg. | Cal. per Sq. M. | According to Rectal Temp. | According to Surface Temp. | | | |
| Morris S. 25 | 9.0 gm. N..... | Continued temperature | 40.0 | 99 | .77 | 1.70 | 51.42 | — 5 | ..... | +48 | | |
| Oct. 24, 1913 | Basal..... | Continued temperature | 39.5 | 101 | .84 | 1.70 | 51.27 | — 2 | ..... | .... | — 0.3 | Oct. 24. |
| 28 | 115.0 gm. glucose.. | Continued temperature | 39.2 | 111 | .93 | 1.64 | 49.35 | + 1 | ..... | .... | + 0.6 | Oct. 29. |
| 29 | Basal..... | Continued temperature | 39.6 | 106 | .79 | 1.62 | 49.04 | — 1 | ..... | +41 | | |
| 31 | 10.3 gm. N..... | Early steep curve..... | 39.1 | 100 | .84 | 1.68 | 50.24 | —11 | ..... | .... | + 2.4 | Oct. 29. |
| Nov. 3 | Restless..... | Early steep curve..... | 38.9 | 108 | .80 | 1.66 | 49.46 | — 9 | ..... | +43 | | |
| 5 | Basal..... | Early steep curve..... | 38.1 | 106 | .81 | 1.60 | 47.31 | — 4 | ..... | +36 | | |
| 17 | Basal..... | First Relapse Ascending temperature | 38.7 | 108 | .81 | 1.44 | 42.52 | — 1 | + 1 | +23 | | |
| 18 | Basal..... | Ascending temperature | 39.9 | 118 | .83 | 1.53 | 45.38 | + 1 | — 1 | +31 | | |
| 24 | Basal..... | Continued temperature | 39.4 | 124 | .76 | 1.79 | 52.69 | —17 | ..... | +52 | | |
| 25 | 8.7 gm. N..... | Continued temperature | 39.2 | 118 | .81 | 1.84 | 54.17 | — 8 | ..... | .... | + 3.9 | Av. Nov. 24 and 26. |
| 26 | Basal..... | Early steep curve..... | 39.1 | 118 | .76 | 1.78 | 51.60 | —17 | ..... | +49 | | |
| Dec. 12 | 10.6 gm. N..... | 7th day, normal temp. | 37.0 | 94 | .84 | 1.45 | 42.89 | — 9 | — 8 | .... | +18.1 | Dec. 13. |
| 13 | Basal..... | 8th day, normal temp. | 37.0 | 83 | .82 | 1.23 | 36.33 | + 0 | + 4 | + 5 | | |
| 15 | 115 gm. glucose.... | 10th day, normal temp. | 37.2 | 95 | 1.01 | 1.36 | 40.07 | — 8 | —11 | .... | + 3.7 | Dec. 16. |
| 16 | Basal..... | 11th day, normal temp. | 37.2 | 88 | .88 | 1.31 | 38.67 | — 2 | + 0 | +11 | | |
| 19 | 115 gm. glucose.... | Second Relapse Ascending temperature | 39.4 | 116 | .93 | 1.60 | 47.46 | + 2 | — 4 | .... | + 1.3 | Dec. 20. |
| 20 | Basal..... | Early steep curve..... | 39.6 | 113 | .78 | 1.61 | 46.83 | — 1 | — 2 | +35 | | |
| 22 | 115 gm. glucose.... | Early steep curve..... | 39.2 | 116 | .94 | 1.55 | 46.04 | +11 | +10 | .... | + 0.7 | Av. Dec. 20 and 26. |
| 23 | Basal..... | Early steep curve..... | 38.3 | 101 | .79 | 1.50 | 44.57 | + 5 | + 2 | +28 | | |
| Jan. 2, 1914 | Basal..... | 8th day, normal temp. | 37.0 | 75 | .81 | 1.17 | 34.93 | + 3 | + 5 | + 1 | | |
| 27 | Basal..... | 33d day, normal temp. | 36.9 | 66 | .82 | 1.10 | 34.30 | + 7 | + 4 | —1 | | |
| Dec. 17, 1914 | Basal..... | One year later..... | 36.8 | 63 | .81 | 1.10 | 35.16 | + 0 | ..... | + 1 | | |
| 18 | 9.6 gm. N..... | One year later..... | 36.9 | 68 | .88 | 1.16 | 37.44 | + 4 | ..... | .... | + 6.5 | Dec. 17, 1914. |

TABLE 7.—Summary of Clinical Calorimetry in Typhoid Fever—(*Continued*)

| Subject and Date | Character of Experiment | Period of Disease | Average Rectal Temp. C. | Average Pulse Rate | Average Respiratory Quotient | Indirect Calorimetry Average per Hour | | Per Cent. Divergence of Direct Cal. from Indirect Calories | | Per Cent. Rise Above Normal Aver. Basal of 34.7 Cal. per Sq. M. | Per Cent. Rise Above Patient's Own Basal Metabolism | Day of Basal Determination Used for Comparison |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Cal. per Kg. | Cal. per Sq. M. | According to Rectal Temp. | According to Surface Temp. | | | |
| Charles F. Nov. 10, 1913 | Basal..... | Ascending temperature | 39.1 | 78 | .79 | 1.44 | 45.26 | — 7 | — 6 | +30 | | |
| 11 | 6.6 gm. N..... | Ascending temperature | 39.2 | 82 | .84 | 1.50 | 47.28 | + 1 | — 2 | .... | + 4.5 | Nov. 10, 1913. |
| 14 | 115 gm. glucose.... | Continued temperature | 39.5 | 97 | .90 | 1.54 | 48.12 | — 8 | — 6 | .... | + 1.3 | Nov. 15. |
| 15 | Basal..... | Continued temperature | 39.9 | 89 | .78 | 1.52 | 47.49 | —10 | — 9 | +37 | | |
| 29 | Basal..... | Early steep curve..... | 36.9 | 83 | .82 | 1.29 | 38.54 | + 2 | ..... | +11 | | |
| Dec. 8 | 10.5 gm. N..... | 7th day, normal temp. | 36.8 | 77 | .92 | 1.38 | 41.53 | — 3 | ..... | .... | +15.5 | Dec. 9. |
| 9 | Basal..... | 8th day, normal temp. | 36.8 | 78 | .92 | 1.20 | 35.96 | + 3 | ..... | + 4 | | |
| 10 | 115 gm. glucose.... | 9th day, normal temp. | 36.7 | 80 | 1.00 | 1.33 | 40.18 | —10 | ..... | .... | +11.7 | Dec. 9. |
| 26 | Basal..... | 25th day, normal temp. | 36.9 | 76 | .85 | 1.17 | 36.36 | + 8 | + 1 | + 5 | | |
| 31 | Basal..... | 30th day, normal temp. | 37.0 | 80 | .79 | 1.21 | 37.52 | — 5 | — 8 | + 8 | | |
| Howard F. Nov. 7, 1914 | Basal..... | Ascending temperature | 39.7 | 103 | 78 | 1.85 | 49.93 | —10 | — 3 | +44 | | |
| 12 | 6.5 gm. N..... | Continued temperature | 39.9 | 105 | .81 | 1.93 | 51.15 | — 2 | + 1 | .... | + 8.9 | Nov. 13. |
| 13 | Basal..... | Continued temperature | 39.8 | 107 | .78 | 1.78 | 47.00 | — 2 | — 2 | +35 | | |
| 20 | Basal..... | Continued temperature | 39.2 | 99 | .76 | 1.76 | 45.52 | — 2 | — 0 | +31 | | |
| Dec. 1 | 115 gm. glucose.... | 5th day, normal temp. | 37.0 | 97 | .97 | 1.54 | 40.10 | — 8 | ..... | .... | +14.1 | Dec. 2. |
| 2 | Basal..... | 6th day, normal temp. | 36.9 | 76 | .94 | 1.35 | 35.15 | + 6 | ..... | + 1 | | |
| 5 | 10.2 gm. N..... | 9th day, normal temp. | 37.1 | 91 | .85 | 1.79 | 47.25 | — 2 | ..... | .... | +24.3 | Dec. 6. |
| 6 | Basal..... | 10th day, normal temp. | 37.0 | 75 | .96 | 1.45 | 38.03 | + 0 | ..... | +10 | | |
| 18 | Basal..... | 22d day,* normal temp. | 37.2 | 107 | .84 | 1.60 | 43.28 | + 1 | + 1 | +25 | | |
| 30 | Basal..... | 34th day,*normal temp. | 37.2 | 108 | .82 | 1.52 | 42.08 | — 2 | + ? | +21 | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Karl S. Jan. 5, 1914 | Basal..... | Continued temperature | 39.9 | 112 | .76 | 1.74 | 54.01 | — 3 | — 6 | +56 | | |
| 6 | 10.5 gm. N..... | Continued temperature | 39.9 | 108 | .82 | 1.88 | 57.93 | + 3 | + 6 | .... | + 7.3 | Jan. 5. |
| 16 | Basal..... | Late steep curve..... | 38.2 | 95 | .79 | 1.57 | 46.76 | ..... | ..... | +35 | | |
| 19 | Basal..... | 1st day, normal temp. | 36.5 | 77 | .88 | 1.19 | 35.83 | ..... | ..... | + 3 | | |
| 21 | 10.0 gm. N..... | 2d day, normal temp. | 36.5 | 72 | .90 | 1.33 | 40.06 | ..... | ..... | .... | +21.1 | Jan. 22. |
| 22 | Basal..... | 4th day, normal temp. | 36.5 | 61 | .89 | 1.10 | 33.08 | ..... | ..... | — 5 | | |
| Feb. 6 | Basal..... | 18th day, normal temp. | 36.9 | 81 | .81 | 1.33 | 40.51 | — 8 | — 6 | +17 | | |
| 7 | 9.6 gm. N..... | 19th day, normal temp. | 37.0 | 90 | .90 | 1.37 | 42.08 | — 5 | + 2 | .... | + 3.9 | Feb. 6. |
| Thomas B. Oct. 15, 1913 | Basal..... | Late steep curve..... | 37.1 | 85 | 82 | 1.07 | 36.54 | — 6 | ..... | + 5 | | |
| 21 | Basal..... | 1st day, normal temp. | 36.9 | 78 | .92 | 0.93 | 31.57 | + 2 | ..... | — 9 | | |
| Richard T. Oct. 18, 1913 | Basal..... | Early steep curve..... | 39.0 | 90 | .81 | 1.69 | 45.44 | — 4 | ..... | +31 | | |
| 20 | Basal..... | Early steep curve..... | 38.3 | 93 | .85 | 1.62 | 43.82 | — 5 | ..... | +25 | | |
| Anton K. Oct. 16, 1913 | Basal..... | Late steep curve..... | 37.1 | 79 | .86 | 1.27 | 38.26 | + 5 | ..... | +10 | | |
| Rose G. Nov. 22, 1913 | Basal..... | 25th day, normal temp. | 37.1 | 78 | .87 | 1.71 | 43.13 | + 1 | ..... | +24 | | |
| Edward B. Oct. 23, 1914 | Basal..... | First relapse: early steep curve | 38.5 | 116 | .79 | 1.43 | 44.33 | — 7 | ..... | +28 | | |
| 26 | 79 gm. olive oil... | First relapse: late steep curve | 37.9 | 118 | .81 | 1.33 | 41.50 | — 2 | ..... | .... | + 3.4 | Oct. 27. |
| 27 | Basal..... | First relapse: late steep curve | 37.6 | 107 | .79 | 1.29 | 40.15 | — 7 | ..... | +16 | | |
| Nov. 4 | Basal..... | 4th day, normal temp. | 37.2 | 104 | .85 | 1.22 | 38.39 | — 3 | ..... | +12 | | |
| 6 | Basal..... | Second relapse: ascending temp. | 39.3 | 124 | .82 | 1.31 | 41.47 | — 5 | ..... | +20 | | |
| 10 | Basal (irrational) | Second relapse: continued temp. | 40.3 | 141 | .76 | 1.67 | 52.18 | — 6 | ..... | +50 | | |
| John K. Dec. 15, 1914 | Basal..... | Continued temperature | 39.2 | 63 | .77 | 1.49 | 48.18 | — 4 | ..... | +39 | | |

* Excluded from averages on account of rapid, irregular and weak heart action.

amounts of heat. Therefore the law of the conservation of energy applies to fever patients.

The rectal temperature does not always give an accurate indication of the average change in body temperature, and better results are often obtained by well covered surface thermometers.

The basal heat production rises and falls in a curve roughly parallel with the temperature. At the height of the fever it averages about 40 per cent. above the normal but in some cases rises to more than 50 per cent. above the normal.

The specific dynamic action of protein and carbohydrate is much smaller in the febrile period of typhoid than in health and in some cases seems to be absent. In convalescence it may be greater than normal.

In a majority of cases a rise in temperature is accompanied by an increasing heat production and an increasing heat elimination.

Typhoid patients can store body fat on an abundant diet while losing body weight and body protein. Loss in weight and loss of protein are usually though not necessarily parallel.

There is a toxic destruction of protein in typhoid fever. This is shown by the fact that patients have a distinctly negative nitrogen balance on a diet which contains more than enough calories to cover the heat production.

The writers wish to express their thanks to their associates, without whose assistance this work would have been impossible. The analyses of food and urine were made by Mr. Frank C. Gephart, with the assistance of Messrs. R. H. Harries, L. C. Mazzola and R. H. Stone; all the electrical measurements in the calorimeter experiments were made by Mr. G. F. Soderstrom. We are indebted to Mr. R. H. Harries and Dr. A. L. Meyer for making the residual analyses of air in the calorimeter experiments and for making most of the calculations, and to Miss G. W. Sims for the painstaking work in checking all these calculations. We are indebted to Miss Estelle Magill and to her assistants, especially Miss A. Honold and Miss M. M. Fauquier, for their skillful administration of the diets and for the collection of the specimens. We wish also to thank Miss M. Sawyer for her aid in the preparation of the charts.

477 First Avenue.

# CLINICAL CALORIMETRY

EIGHTH PAPER

## ON THE DIABETIC RESPIRATORY QUOTIENT*

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The respiratory quotient, or the ratio of the volume of carbon dioxid expired to the volume of oxygen inspired, in the case of protein oxidation is stated by Loewy[1] to be 0.801. This relation depends on the net result of the oxidation of the many amino-acids of which protein is composed. It is apparent that when some of these amino-acids are converted into glucose which is eliminated in the urine, the respiratory quotient for protein will not hold true. It has been shown[2] that the carbon of glycocoll and alanin is completely converted into glucose in the diabetic organism, and that three of the carbon atoms which are contained in aspartic and glutamic acids are similarly convertible into glucose. Dakin[3] states that prolin and arginin yield glucose comparable in quantity to that yielded by glutamic acid. According to this author cystin and serin also yield glucose.

The reactions involving the conversion of amino-acids into sugar and urea may thus be written:[4]

Glycocoll .....$6CH_2NH_2.COOH + 3CO_2 + 3H_2O = 2C_6H_{12}O_6 + 3CH_4N_2O + 3O_2$

Alanin .....$2CH_3.CHNH_2.COOH + CO_2 + H_2O = C_6H_{12}O_6 + CH_4N_2O$

Aspartic Acid.....$2COOH.CH_2.CHNH_2.COOH + H_2O = C_6H_{12}O_6 + CH_4N_2O + CO_2$

Glutamic Acid.....$2COOH.CH_2.CH_2.CHNH_2COOH + 3O_2 = C_6H_{12}O_6 + CH_4N_2O + 3CO_2 + H_2O$

Prolin .....$2CH_2.CH_2.CH_2.CH.COOH + 5O_2 = C_6H_{12}O_6 + CH_4N_2O + 3CO_2 + H_2O$ (NH)

Arginin .....$2NH_2.C.NH.CH_2.CH_2.CH_2.CHNH_2COOH + 5O_2 = C_6H_{12}O_6 + 4CH_4N_2O + 2CO_2$ (NH)

Osborne and Jones[5] have reported an analysis of 100 grams of ox meat containing 16.18 per cent. of total nitrogen. This analysis will

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* From the Russell Sage Institute of Pathology, in Affiliation with the Second Medical Division of Bellevue Hospital, New York City.

1. Loewy: Handb. d. Biochem., 1911, iv, No. 1, 279.
2. Ringer and Lusk: Ztschr. f. physiol. Chem., 1910, lxvi, 106.
3. Dakin: Jour. Biol. Chem., 1913, xiv, 321.
4. For more complete theoretical details consult: Lusk, Jour. Am. Chem. Soc., 1910, xxxii, 671; and Dakin and Dudley, Proc. Seventeenth Internat. Cong. Med., 1914, Sec. ii, Part II, 127.
5. Osborne and Jones: Am. Jour. Physiol., 1909, xxiv, 438.

be found below together with the respiratory quotients, both normal and diabetic, of the individual amino-acids.

TABLE 1.—Analysis of 100 Grams Ox Meat with Respiratory Quotients

| Substance | In 100 Gm. Meat gm. | Respiratory Quotient | |
|---|---|---|---|
| | | Normal | Diabetic |
| Glycocoll | 2.06 | 1.00 | * |
| Alanin | 3.72 | 0.83 | * |
| Valin | 0.81 | 0.75 | |
| Leucin | 11.65 | 0.73 | |
| Prolin | 5.82 | 0.82 | 0.60 |
| Phenylalanin | 3.15 | 0.87 | |
| Aspartic acid | 4.51 | 1.17 | † |
| Glutamic acid | 15.49 | 1.00 | 1.00 |
| Serin | ? | .... | |
| Tyrosin | 2.20 | 0.89 | |
| Arginin | 7.47 | 0.73 | 0.40 |
| Histidin | 1.76 | 0.90 | |
| Lysin | 7.59 | 0.71 | |
| Ammonia | 1.07 | | |
| Tryptophan | Present | 0.87 | |
| Total | 67.30 | | |

* R. Q. depressed below that of fat if glycocoll or alanin be ingested.
† R. Q. increased above that of fat if aspartic acid be given.

A glance at the above table shows how the respiratory quotient of 0.801 for protein is based on the sum of the results of the oxidation of many different substances, and also that the respiratory quotients usually tend to fall when certain of the amino-acids are converted into sugar.

A clear idea of this fall in the respiratory quotient can only be obtained if the respiratory metabolism of those amino-acids which are convertible into glucose is contrasted, the normal with the diabetic condition.

It will be noted in the foregoing table that only 67 per cent. of the ox protein was recovered as amino-acids. This is explained by the deficiency in the method; for Osborne and Jones[6] have analyzed a specially prepared mixture containing known quantities of a large number of amino-acids and have recovered only 66 per cent. of the substances present. As regards those amino-acids which are convertible into glucose, the following percentages were recovered from the mixture: Alanin, 46 per cent., prolin 73 per cent., aspartic acid, 42.5 per cent., glutamic acid 69 per cent., arginin 65 per cent. If one assumes that the quantity of glycocoll is at least double that found,

6. Osborne and Jones: Am. Jour. Physiol., 1910, xxvi, 325.

one arrives at values from which one may compute the quantity of sugar which should in theory arise from these acids. This appears in Table 2.

Since the 100 gm. of the ox muscle analyzed contained 16.18 gm. of nitrogen, the D:N equals 2.75:1.

TABLE 2.—Calculation Showing the Origin of Glucose from Protein

| Substance | Osborne | Recalculated | Glucose |
|---|---|---|---|
| Glycocoll ..... | 2.06 | 4.0 | 3.2 |
| Alanin ..... | 3.72 | 8.1 | 8.2 |
| Aspartic acid .... | 4.51 | 10.6 | 7.2 |
| Glutamic acid .... | 15.49 | 22.3 | 13.6 |
| Prolin ..... | 5.82 | 8.0 | 6.3 |
| Arginin ..... | 7.47 | 11.5 | 5.9 |
| | | 64.5 | 44.4 |

TABLE 3.—Respiratory Exchange in the Normal and Diabetic Condition of Six Amino-Acids, as they are Contained in 100 Gm. of Ox Meat, and which are Convertible into 44.4 Gm. of Glucose, D:N = 2.75

| Substance | Grams | Normal | | Diabetic | | | |
|---|---|---|---|---|---|---|---|
| | | | | Oxygen | | Carbon Dioxid | |
| | | Oxygen gm. | Carbon Dioxid gm. | Absorbed gm. | Eliminated in Reaction gm. | Absorbed in Reaction gm. | Eliminated gm. |
| Glycocoll ... | 4.0 | 2.56 | 3.52 | ..... | 0.85 | 1.17 | |
| Alanin ..... | 8.1 | 8.75 | 10.01 | 0.0 | ..... | 2.00 | |
| Aspartic acid | 10.6 | 7.65 | 12.27 | 0.0 | ..... | .... | 1.75 |
| Glutamic acid | 22.3 | 21.85 | 30.04 | 7.30 | ..... | .... | 10.03 |
| Prolin ..... | 8.0 | 12.25 | 13.77 | 5.57 | ..... | .... | 4.59 |
| Arginin ..... | 11.5 | 11.63 | 11.63 | 5.32 | ..... | .... | 2.91 |
| | | | | 18.19 | 0.85 | 3.17 | 19.28 |
| | | | | 0.85 | .... | .... | 3.17 |
| | 64.5 | 64.69 | 81.24 | 17.34 | | | 16.11 |
| R. Q. | | | 0.915 | | | 0.675 | |

When the D:N ratio is 3.65, 59 gm. of glucose, or 14.6 gm. more than the quantity above estimated, are eliminated in the urine when 100 gm. of protein are destroyed. These 14.6 gm. represent an additional amount of glucose whose origin is unexplained and which is equal to 24 per cent. of the total maximal production. Such sources of sugar might be cystin, which if all the sulphur in protein were in that form

might at most yield 2 gm. of glucose and serin whose solubility has prevented any accuracy of determination.

Having determined the approximate quantities of the various sugar yielding amino-acids, one may now compute the difference between their oxidation normally and in the diabetic. This is shown in Table 3.

This table signifies that when glycocoll, alanin, aspartic acid, glutamic acid, prolin and arginin, together aggregating nearly two-thirds by weight of the protein complex, are oxidized in the normal organism in the proportion in which they may exist in meat, the respiratory quotient is 0.915, whereas if 44.4 gm. of glucose is formed from them the respiratory quotient sinks to only 0.675.

Of those amino-acids which do not yield glucose, three, valin, leucin and lysin, which together aggregate 20 gm. according to Osborne's (uncorrected) analysis of 100 gm. of meat, have respiratory quotients of 0.75, 0.73 and 0.71, respectively, whereas three others, phenylalanin, tyrosin and histidin, together amounting to only 7.1 gm., yield respiratory quotients of 0.87, 0.89 and 0.90. Furthermore, the 1.07 gm. of ammonia liberated would tend to reduce the quotient through urea formation. It is therefore obvious that the respiratory quotient for protein in diabetes is made up predominately of the oxidation of the remnants of the sugar forming amino-acids and from the oxidation of other amino-acids having in the main respiratory quotients of 0.75 to 0.71. As actually calculated, the above named mixture of non-sugar producing amino-acids would yield 48.25 gm. of $CO_2$ and require 45.86 gm. of oxygen for oxidation, showing a respiratory quotient of 0.76.

The aggregate quotient of the non-sugar forming amino-acids as set forth above may be indirectly obtained by deducting the estimated respiratory exchange of the sugar-forming amino-acids from that of the total involved in the normal oxidation of 100 gm. of ox protein, as shown in Table 4.

TABLE 4.—Aggregate Quotient of Non-Sugar Forming Amino-Acids

| | Oxyen gm. | Carbon Dioxid gm. | Resp. Quot. |
|---|---|---|---|
| Normal oxidation of 100 grams of beef protein | 138.18 | 152.17 | 0.801 |
| Estimated oxidation of the sugar forming amino-acids | 64.69 | 81.24 | 0.915 |
| | 73.49 | 70.93 | |
| Add $CO_2$ for urea formation from 1.07 gm. $NH_3$ | ..... | 1.39 | |
| Estimated oxidation of non-sugar forming amino-acids | 73.49 | 72.32 | 0.716 |

Although the last respiratory quotient 0.716 closely approximates that of leucin (0.73) and lysin (0.71), the dominant non-sugar forming amino-acids, it is evident that the influence of the other non-sugar

forming amino-acids would tend to raise the quotient to a higher level, to 0.76 in the before mentioned calculation. Therefore, the present figures can only be regarded as an attempted solution of the problem rather than as a precise analysis.

When the mixture of six sugar-forming amino-acids, aggregating 64.5 gm., is normally oxidized

$$O_2 = 64.69 \text{ gm. and } CO_2 = 81.24 \text{ gm.}$$

and when it is converted into 44.4 gm. of glucose

$$O_2 = 17.34 \text{ gm. and } CO_2 = 16.11 \text{ gm.}$$

the difference between these two sets of figures will represent the quantities of respiratory gases which would not be involved in the respiratory exchange in diabetes and would amount to

$$O_2 = 47.35 \text{ gm. and } CO_2 = 65.13 \text{ gm.}$$

If one takes the grams of respired gases in the normal combustion of 100 grams of protein as given by Loewy, and deducts from these the quantity not eliminated according to the above computation, one arrives at the following results for the diabetic respiratory quotient:

TABLE 5.—PROTEIN RESPIRATORY QUOTIENT WITH D:N = 2.75

| | Oxygen gm. | Carbon Dioxid gm. |
|---|---|---|
| Normal oxidation 100 grams beef protein | 138.18 | 152.17 |
| Deduct for intermediary production of 44.4 grams of glucose | 47.35 | 65.13 |
| | 90.83 | 87.04 |

R. Q. = 0.697.

Proceeding now to the consideration of the cases of diabetes in which the D:N is 3.65, calculations have been made the relations of which may be thus presented:

TABLE 6.—PROTEIN RESPIRATORY QUOTIENT WITH D:N = 3.65

| | Oxygen gm. | Carbon Dioxid gm. |
|---|---|---|
| (1). Normal oxidation of 100 grams of beef protein | 138.18 | 152.17 |
| Deduction, if 16.28 grams N × 3.65 = 59.41 glucose | 63.38 | 87.15 |
| | 74.80 | 65.02 |

R. Q. = 0.632.

The respiratory quotient for fat is 0.707, and since fat forms the main recourse of the diabetic, the respiratory quotient will be found nearer to that of fat than to 0.632 for protein. Thus, in a diabetic dog with a D:N ratio of 3.54 in which 23 per cent. of the total heat production was derived from protein and 77 per cent. from fat, the

respiratory quotient was 0.687, the non-protein respiratory quotient being 0.704, which closely approximates that of fat. In the case of a diabetic patient with a low protein metabolism whose urinary D:N was 3.6, Du Bois has found during a three hour period a respiratory quotient of 0.697. In another diabetic man with approximately the same D:N ratio but whose protein metabolism was higher (13 per cent. of the total energy) the R. Q. was 0.691.

Magnus-Levy[7] has called attention to a possible reduction in the respiratory quotient when beta-oxybutyric acid is formed from fat. He estimates that the maximal quantity of beta-oxybutyric acid derivable from 100 gm. of fat is 36 gm. Under these circumstances, the respiratory quotient for fat would be reduced from 0.707 to 0.669. The case is not so simple, however, for if the 36 gm. of acid formed neutralized sodium bicarbonate, 15.23 gm. of carbon dioxid would be eliminated.

These relations are shown in Table 7:

TABLE 7.—THEORETICAL RESPIRATORY QUOTIENT WITH BETA-OXYBUTYRIC ACID FORMED FROM FAT

| | Oxygen Liters | Carbon Dioxide Liters | R. Q. |
|---|---|---|---|
| 100 gm. fat | 201.9 | 142.73 | 0.707 |
| 36 gm. beta-oxybutyric acid | 34.85 | 30.96 | 0.889 |
| | 167.05 | 111.77 | 0.669 |
| Add for 15.23 gm. $CO_2$ from $NaHCO_3$ | | 7.74 | |
| Possible end result | 167.05 | 119.51 | 0.715 |

Since other bases than sodium bicarbonate may be used for the neutralization of beta-oxybutyric acid, it is apparent that the exact determination of the theoretical respiratory quotient when this acid is produced in large amounts in human diabetes is at present impossible.

This discussion has been prepared in order to further the understanding of a forthcoming description of metabolism in diabetes mellitus.

7. Magnus-Levy: Ztschr. f. klin. Med., 1905, lvi, 83.